VOLUME 4 MARCH, 1963 NO. 2

THOMAS P. HAYNIE, AND WILLIAM H. BEIERWALTES, M.D. Hematologic Changes Observed Following I^{131} Therapy for Thyroid Carcinoma 85

RUTH C. STEINKAMP, M.D., JOHN H. LAWRENCE, M.D., AND JAMES L. BORN, M.D. Long Term Experiences with the Use of P^{32} in the Treatment of Chronic Lymphocytic Leukemia 92

ARTHUR C. BEALL, JR., M.D. AND PHILIP C. JOHNSON, M.D. Use of the Radioisotope Renogram in the Differential Diagnosis of Renal Insufficiency Following Vascular Surgery 106

FELIX J. PIRCHER, M.D., EDWARD A. CARR, JR., M.D., AND MARY ELLEN PATNO, PH.D. Evaluation of Quantitative Aspects of the Radioisotope Renogram 117

L. VAN MIDDLESWORTH, M.D., PH.D., JO AUBREY TURNER, B.S., AND ALYS LIPSCOMB, M.D. Liver Function Related to Thyroxine Metabolism 132

JOSEPH L. RABINOWITZ, PH.D., BERNARD SHAPIRO, M.D., AND PHILIP JOHNSON, M.D. "Sephadex Chromatographic" Test in the Evaluation of Thyroid Function 139

DAVID L. JOFTES, PH.D. Radioautography, Principles and Procedures 143

LEOPOLDO J. ANGHILERI, PH.D. A Chromatographic Study of the Stability of Iodine-131 Labeled Sodium o-Iodohippurate 155

H. W. WEIGEL, M.D., J. PARSONS, M.D., H. ELRICK, M.D., C. J. HLAD, JR., M.S., E. MILLER, M.S. The Excretion of Na^{22} in Sweat 159

R. T. MORRISON, M.D., J. A. BIRKBECK, M.B., CH.B., T. C. EVANS, PH.D., J. I. ROUTH, PH.D. Radioiodine Uptake Studies in Newborn Infants 162

VOLUME 4 MAY, 1963 NO. 3

Program—Tenth Annual Meeting 169

Abstracts—Tenth Annual Meeting 181

Technical Exhibitors 218

Scientific Exhibitors 220

President's Annual Report 223

Officers, Executive Committee and Board of Trustees 225

Professor Emilio Segré—Fourth Annual Nuclear Pioneer Lecture in honor of Professor Enrico Fermi 227

W. H. Oldendorf, M.D. and M. Kitano, M.D. Selenomethionine Reappearance in Blood Following Intravenous Injection 231

A. S. McFee, M.D., N. B. Ackerman, M.D., and M. K. Loken, Ph.D., M.D. The Prevention of Hepatic Metastasis by the Use of a Colloidal Suspension of Radioactive Chromic Phosphate ($CrP^{32}O_4$) 234

F. H. Foeckler, Jr., Sc.D., N. M. Bering, M.T. (ASCP), J. Siragusa, M.T., (ASCP), and O. B. Hunter, Jr., M.D. Comparative Thyroid-Function Studies with the Resin T-3 Test. 239

M. A. Razzak, M.D. The Use of a Modified Radioactive Test for Evaluating The Peripheral Circulation. 244

VOLUME 4 **JULY, 1963** **NO. 4**

Raymond G. Rose, M.D., James E. Hartfield, M.D., Mavis P. Kelsey, M.D., and Eleanor J. MacDonald, A.B. The Association of Thyroid Cancer and Prior Irradiation in Infancy and Childhood. 249

Ismael Mena, M.D., Pablo Thomsen, M.D., and Leslie R. Bennett, M.D. Determination of Coronary Blood Flow Index by External Scintillation Detection. 259

Paul V. Harper, M.D., Warren D. Siemens, Katherine A. Lathrop, M.S., and Harold Endlich, M.D. Production and Use of Iodine-125. 277

Murray L. Janower, M.D. A Query Into the Use of Tracer Doses of I^{-131}. 290

Milton G. Crane, M.D., John E. Holloway, M.D., Ralph Adams, B.A., and Ivor C. Woodward, M.A. The Relative Mean Transit Times of Red Cells and Plasma in the Portal Circulation of the Dog. 296

Barney T. Watson, M.A. Computers in Activation Analysis 306

Franklin T. Brayer, M.D. Influence of Plasma from a Variety of Stressed Animals on I^{131} Uptake in Chick Embryos. 312

J. U. Schlegel, M.D., R. M. O'Dell, Ph.D., and J. L. Izenstark, M.D. Importance of Stop Flow to Kidney Scans. 320

Hal O. Anger, B.S. and Alexander Gottschalf, M.D. Localization of Brain Tumors with the Positron Scintillation Camera 326

VOLUME 4 SEPTEMBER, 1963 NO. 5

D. Bruce Sodee, Major, MC A New Scanning Isotope, Mercury^{197} A Preliminary Report. 335

Hyo H. Byun, M.D., Gisela Albrecht, M.D., George W. Holmes, M.D. and Robert Landauer, Ph.D. Pulmonary Function Test Using Krypton-85. 345

Walter DiGiulio, M.D., Paul Weinhold, Ph.D., and George E. Thoma, Jr., M.D. The Thyroxin-Protein Dissociation Index, A Modified T_3 Resin Uptake Procedure. 359

Gerald J. Hine, Ph.D., Melvin H. Farmelant, M.D., John A. Cardarelli, M.A. and Belton A. Burrows, M.D. Four Channel Magnetic Tape Recording and Digital Analysis of Radio-Hippuran Renal Function Tests in Normal Subjects 371

Cleamond D. Eskelson, M.D., Arthur L. Dunn, Ph.D., Richard E. Ogborn, M.D. and John F. McLeay, M.D. Distribution of Some Radioiodinated Tetracyclines in Animals. 382

P. C. Johnson, M.D. and T. R. Redding, B.S. Glucose-1-C-14 Oxidation by Blood: A Potential Test for Tissue Effects of Thyrotoxicosis. 393

William H. Oldendorf, M.D. Supplementing the Rate Meter by Adding an Efficient Low-Pass Filter. 399

G. V. Taplin, M.D., E. K. Dore, M.D., and D. E. Johnson, M.D. The Quantitative Radiorenogram for Total and Differential Renal Blood Flow Measurements 404

Leopoldo J. Anghileri, Ph.D. A Study of the Stability of Neohydrin (3-Acetoxymercuri-2-Methoxypropylurea) Labeled with Mercury-203. 410

Current Abstracts in Nuclear Medicine 413

President's Letter 415

VOLUME 4 NOVEMBER, 1963 NO. 6

MILLARD N. CROLL, M.D., LARRY H. SHUMAN, M.D., LEONARD STANTON, M.S. AND CASIMIR CZARNECKI, M.D. Radioisotope Placentograph: A Bedside Procedure. 417

H. HOROWITZ, M.D., J. G. KEREIAKES, PH.D., E. L. SAENGER, M.D. AND THEODORE SELKIRK, JR., M.D. Liquid Scintillation Counting of I^{131} in a Clinical Laboratory. 426

GERALD J. HINE, M.D. Color-Coded Digital Print-Out for Radioisotope Scanning. 439

ROBERT C. MEADE, M.S., M.D. AND DONALD A. FRANKLIN, M.D. Results of a Standardized Hippuran Renogram. 446

JOHN E. KEARNS, M.D. AND WILLIAM HUTSON, M.D. Tagged Isomers and Analogues of Thyroxine (Their Transmission Across the Human Placenta and Other Studies). 453

F. S. EBERTS, JR., AND E. P. MARKOVICH. A Digital-Computer Method for Rapid Radioactivity Calculations. 462

C. T. HOWE AND R. P. EKINS. The Bromide Space After the Intravenous Administration of ^{82}Br. 469

E. JAMES POTCHEN, M.D. Isotopic Labeling of the Rat Parathyroid as Demonstrated by Autoradiography. 480

RALPH J. GORTEN, M.D., AND HARRY M. HUGHES, PH.D. Extrapolation of Precordial Counting Curves (Preliminary Progress Note) 485

Index 487

President's Letter vii

Editorial Page ix

First Call for Papers xiii

STATEMENT OF OWNERSHIP, MANAGEMENT AND CIRCULATION

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I *Samuel N. Turiel, Managing Editor* of the *Journal of Nuclear Medicine*, certify that the statements made above are correct and complete.

JOURNAL OF NUCLEAR MEDICINE 4:1-8, 1963

An Appraisal of As-74 for Localization of Brain Tumours

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Toronto

INTRODUCTION

This study was undertaken to provide an independent evaluation of the use of As-74 for external localization of space occupying intracranial lesions. The advantages of a positron emitting radioisotope for localization purposes were described as early as 1951 by Wrenn (1) and Sweet (2), but the first publication describing the method was published by Brownell and Sweet (3) in 1953. After some preparation which included instrument design, separation of As-74 by methods other than that used by Brownell and a preliminary series of scans which is not included here, the present series of patients was begun.

INSTRUMENTATION

The moving mechanical system and recording plate duplicate the second model of Brownell and Sweet. The detecting heads, collimation, and circuitry differ in some respects and are therefore described.

The 1½" by 1" Na I (Th) crystals are used with a pair of Dumont 6292 photomultipliers and fitted with an inverted cone collimator (Fig. 1). The purpose of the configuration in the shielding was to shorten the elongated oval isosensitivity curve characteristic of coincident connected detecting heads and to benefit from the enlarged solid angle made available by larger crystals. This arrangement of course reduces the positrocephalogram (PCG) response in lateral positions but the very sensitive asymmetrogammagram (AGG) more than makes up for the deficiency.

The phototube output yields a 0.6 microsecond pulse with a 0.2 microsecond rise time. The 0.6 microsecond pulse is amplified and applied to a Schmidt discriminator adjusted to pass pulses corresponding to 0.3 Mev and over. The fast rise time is preserved for the input to the coincident circuit and enters as a 70 volt pulse.

The coincident pulses are scaled by a factor of 10 before printing. The asymmetry circuit receives its signal from a pair of scalers (160:1), and then registers an excess of 800 counts in either direction by a curved (right) or straight (left) directional marker.

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The As-74 used in the earlier work was separated in Toronto from a Germanium target irradiated in Birmingham, England, and prepared for intravenous administration as Sodium Arsenite. The radioactive Arsenic used for the last three years was obtained from Abbot Laboratories, Oak Ridge, Tenn. as their parenteral preparation in the form of Sodium Arsenate.

PROCEDURE

Patients were chosen for the study on a somewhat variable basis depending on conditions existing on the arrival of a shipment of Arsenic. All the patients were brain tumour suspects, some with a history of special investigation, and some with scheduled special investigation or operation. Patients were at times held for the test, both as outpatients and inpatients, while at other times candidates were chosen from among brain tumour suspects in hospital after the arrival of the shipment. It follows then that a few patients were diagnosed before scanning and were already scheduled for surgery, while others were treated according to the outcome of the Arsenic Scan.

The patient to be scanned was given from 1 to 1.5 mc of As-74 intravenously in an antecubital vein about twenty minutes before the scan was to be begun, and the syringe rinsed by one or two withdrawals of blood which were then returned to the vein. Extravascular infiltration occurred in a few cases and in these a waiting period of about two hours was required to remove the effect of the As-74 excess in one arm. The performance of the scan required from thirty to forty minutes with a horizontal scanning speed of 0.2 cm/sec. The records were read as soon as possible with no knowledge of the patient or diagnostic opinion to that time. Correlation with clinical findings was not ruled out for the final report, but it was felt that more objective assessments were obtained when the first observation was made without prejudgement. An earlier study[1] had indicated that knowledge of the diagnostic opinion at the time of scanning served

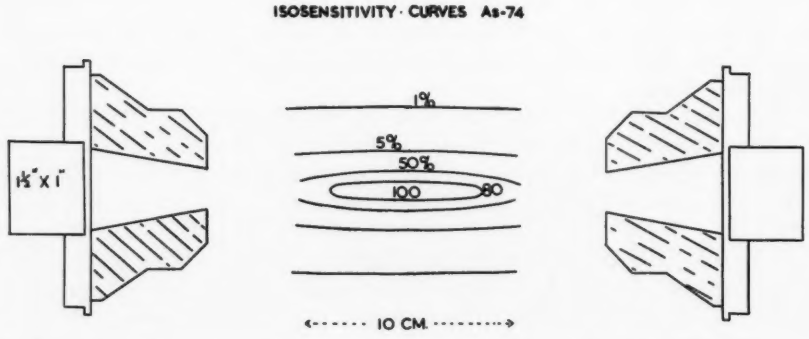

Fig. 1. Isosensitivity curves of the coincidence system determined with a "point" source in a water phantom.

[1]Presented to a meeting of the Canadian Association of Radiologists, Nuclear Medicine Session, Jan. 15, 1958.

only to add some suspicious sites to a negative report, or more often, to discount a suspicious area. In no case did the clinical opinion serve to turn a doubtful reading into a positive one.

In some cases where the finding was doubtful, on the borderline between positive and negative, or where the record was faulty for a technical reason, the scan was repeated, usually within four hours. The dose given (average 1.2 mc) was calculated to be just sufficient to yield a satisfactory density on the records. Since Arsenic is rapidly excreted from the body there is too little activity left in 24 hours to provide good contrast in most patients. Repeat scans were therefore performed as soon as possible. A recent publication by Mealey (4) provides evidence that glioblastomas have a longer retention period than the meningiomas so that repetitions 24 hours or later might have been useful.

The criterion for a positive localization was rather rigid. Fig. 2 is a photograph of a positive scan with the obvious localization both on PCG and ACG in a patient with a meningioma. Fig. 3, a reproduction of the scan on a patient with a glioblastoma represents about the lower limit of the positive findings. Any records less marked than these would be considered negative, negative (suspicious), or questionably positive. Fig. 4 shows a good normal distribution and was performed on a patient shown to have no cerebral neoplasm (optic atrophy).

RESULTS

Patients scanned over the last 18 months were considered in detail. These are consecutive scans, the only cases rejected being the few in which there are incomplete or otherwise faulty records. Of 132 patients with adequate data there were 35 verified supratentorial brain tumours (Table I). The remaining 97 cases included 64 where the disease was still in question, many of them brain tumor suspects. Twenty-nine fully diagnosed cases are set out in Table II. The asterisked numbers in the "positive" column are graded as "single plus" or con-

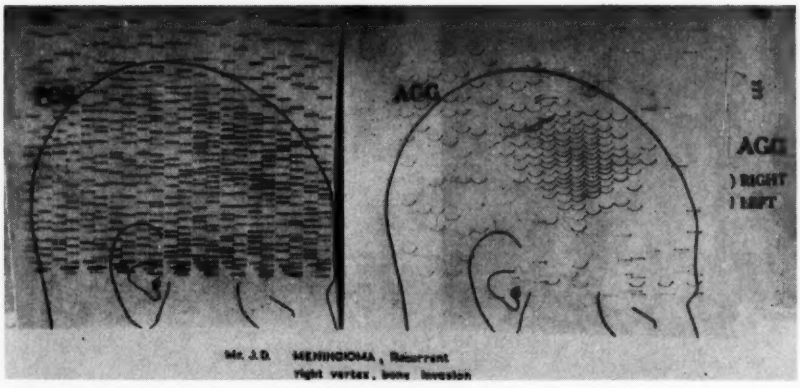

Fig. 2. PCG and AGG of patient with a meningioma.

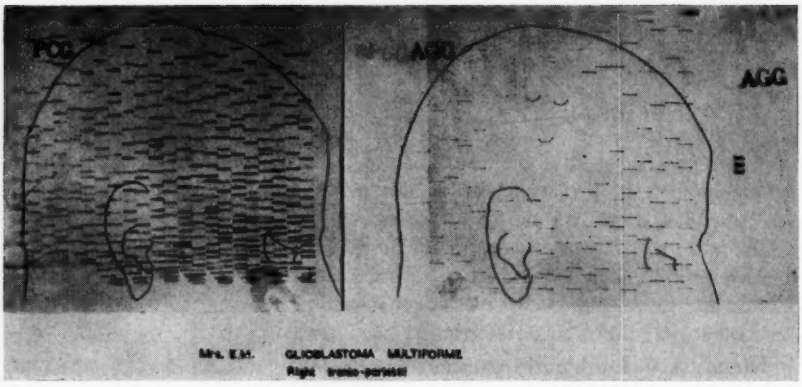

Fig. 3. Right sided glioblastoma. This scan was judged to be a positive finding on the strength of the regular gradation of markers on the AGG.

centrations with some question as to boundary and they are all associated with vascular disturbances. The one pseudo-tumor with a clear localization simply indicated the presence of a week-old scalp incision. The latter type of patient was ordinarily not scanned. This one case was scanned and the record read and reported without reference to the patient's history and without a notation on the scanning chart as to the existence of a visible lesion. The relationship to the recent incision was of course immediately apparent to the surgeon on reading the report, but since it was reported as a positive finding it is included here as such.

The remaining scans are all negative except for an accurately localized subdural haematoma and two cases of generalized cerebral atrophy. The latter two records show a patchy appearance both in the positrocephalogram and the asymmetrogammagram presumably corresponding to the irregular blood supply

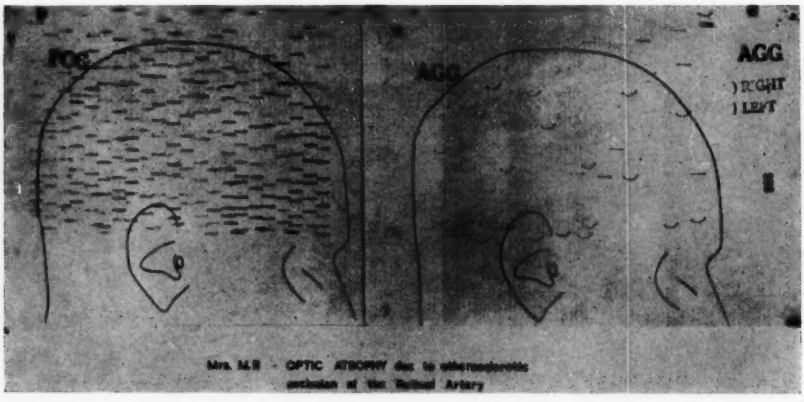

Fig. 4. A typical normal scan.

to the brain. They were not easily mistaken for the well defined localization of an abcess, tumour, or the above-mentioned subdural haematoma.

For the analysis of verified supratentorial brain tumors a larger consecutive series of 195 cases was used. In 60 of these cases there were supratentorial brain tumours verified by microscopic examination, which were then analysed further according to the pathological finding. A summary of the analysis is set out in Table III.

On examination of Table III it would appear that meningiomas result in a consistently high local concentration of Arsenic. The one meningioma that was missed occurred when a particularly low dose was given and the tumour was well down in the temporal area. Some of the glioblastoma multiforme presented a marked concentration equal to that taken up in a typical meningioma, yet more than half are negative. This is in contrast to the finding of Sweet and Brownell (5) who recognized "abnormal concentration" in 38 out of 42 glioblastomas. The same trend is true of uptake in tumours labelled as astrocytomas. Sweet and

TABLE I

AS-74 SCANS 132 CONSECUTIVE CASES

Fully Diagnosed, Brain Tumour Excluded	29
Undiagnosed, Including Unverified Brain Tumours	64
Verified Supratentorial Brain Tumours	35
Cases Excluded, Verified Brain Tumours	4

TABLE II

29 CASES FULLY DIAGNOSED
BRAIN TUMOUR EXCLUDED

	Arsenic Scan Finding	
	Negative	*Positive*
2 Cerebral Abscess	1	1
1 T.B. Abscess	1	0
6 Cerebral Infarcts	4	2*
1 Intracranial Clot	0	1*
1 A-V Malformation	1	0
1 Subdural Hydroma (Old) and Subdural Haematoma	0	1
4 Pseudo-Tumours	3	1 (Scalp Incision)
2 Stenosis of Aquaduct	2	0
1 Arnold-Chiari Malformation	1	0
3 Encephalitis	3	0
2 Hepatic Coma	2	0
2 Generalized Cerebral Atrophy	0	2
1 Aneurysm, Vertebral Artery	0	1*
1 Parkinson's Disease	1	0
1 Motor Neuron Disease	1	0

*See text section results.

TABLE III

60 VERIFIED SUPRATENTORIAL BRAIN TUMOURS CLASSIFIED BY PATHOLOGICAL FINDING

	Scan	
	Negative	*Positive*
Glioblastoma Multiforme	11	8
Malignant Glioma	2	4
Secondary Carcinoma	1	1
Fibrosarcoma	0	1
Hodgkins Disease	1	0
Teratoma	0	1*
Xanthogranuloma	0	1
Benign Gliomas, Astrocytoma and Astrocytoma and Oligodendroglioma	7	2
Sellar and Suprasellar Tumours	3	0
Meningioma	1	16

Brownell located 10 out of 14, whereas we could localize only 2 out of 9. The other categories have not appeared in great enough number to warrant direct comparison.

DISCUSSION

Of the verified tumours only 33, or 55 per cent, were located, compared to Sweet and Brownell's overall "accuracy" of 75 per cent. Divided according to the pathological findings, meningiomas are followed by glioblastomas multiforme and the less malignant gliomas in order of their one hour uptake of Arsenic. On the whole the order set out by Sweet and Brownell (5) and Mealey et al (4) were confirmed although there were too few secondary carcinomas to support their placement between gliobastomas and astrocytomas.

The larger proportion of abnormal, or positive scans found by Sweet and Brownell may be due to higher instrument sensitivity, or to a somewhat larger dose of Arsenic-74 given to the patient, but it is more likely due to the difference in the arbitrary line drawn by the reader between a definite positive and the questionable or normal reading.

The appearance of the record is the net result of several variables, the most important of which is the degree to which the radioisotope in its particular chemical form concentrates in various types of lesions in the brain. The arrangement, size, collimation, and sensitivity of the detecting heads are determining factors. So is also the method of recording with its inherent ability to present as a contrasting density of printed markers the range of concentration of the radioisotope in the brain of the patient.

Experiments with phantoms on our apparatus indicate that the target, non-target ratio must be 2.5:1 to obtain minimal contrast, in the concentration range

found in patients. Larger crystals may improve the sensitivity for the AGG but will at the same time reduce resolution in the PCG. The recording system with its black on white presentation uses no form of "background erase" or similar contrast heightening device, and this, in the view of the authors, represents a possible site for improvement in the positron-annihilation system of scanning.

This study would suggest that there is a wide range of concentrating ability of sodium arsenate associated with the different kinds of neoplasms. It also appears that by drawing a rather stringent criterion as to the definite existence or only questionable existence of a localization of Arsenic-74 a useful purpose can be served. First, it has presented us with a complete omission of falsely positive findings. In view of the growing reliability of the scan the surgeon can be quite confident that a positive localization definitely represents the site of a neoplasm, an abscess, or some condition which warrants further investigation. In addition, the absence of a definite localization when a meningioma is expected provides a good probability that the lesion is not a meningioma.

It must be emphasized that the present study was designed to evaluate the use of Arsenic-74 as a diagnostic aid in its own right and as mentioned before under a certain set of local conditions. It does not lend itself to a direct comparison with results using I-131 human serum albumin and single ended focussing collimators. The authors propose to proceed with a direct comparison in the near future.

The scintillation crystals used for this series of patients should have heightened the sensitivity for mid-line localization over those placed laterally. The isosensitivity curves obtained (Fig. 1) indicate that this indeed is so, but there are no cases which would clearly show the effect of the physical change in the detecting heads. We can only presume that it was helpful in locating the deep or mid-line tumours.

It is interesting to note that in three cases (2 glioblastoma multiforme, 1 malignant glioma) the scans were positive in the presence of negative air

TABLE IV

SUMMARY OF POSITIVE LOCALIZATIONS

Arsenic–74—Indispensable in 3 Cases	
	2 Glioblastoma Multiforme
	1 Malignant Glioma
Arsenic–74—Sole Special Investigation	
	3 Meningiomas
	1 Malignant Glioma
	2 Glioblastoma Multiforme
	1 Fibrosarcoma
In Retrospect, Arsenic–74—Sole Special Investigation Necessary	
	8 Meningioma
	2 Glioblastoma Multiforme
	1 Malignant Glioma

study and arteriogram; in seven cases the scan was sufficiently clear to proceed without using other special investigation; in eleven cases, in retrospect, the Arsenic scan was clear enough to have proceeded without the aid of additional special investigations such as arteriograms (Table IV).

SUMMARY

Arsenic-74 may be used to provide useful information in the diagnosis of intracranial space occupying lesions. The high degree of specificity, in our hands, for meningiomas may be put to good use in ruling out the likelihood of this particular type of neoplasm in certain patients.

The overall successful localization of intracranial tumours and abscesses is slightly lower than that reported by Sweet and Brownell. Meningiomas are rarely missed, but the lower proportion of successful findings in certain gliomas may be explained by the smaller average dose given to the patient, and insistence on a readily discernable contrast on the records for a positive reading.

ACKNOWLEDGEMENTS

We are indebted to Mr. M. Timanoff for technical assistance in the carrying out the scans as well as for the construction of much of the electronic equipment. This work is supported by grants from the Ontario Cancer Treatment and Research Foundation.

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JOURNAL OF NUCLEAR MEDICINE 4:9-17, 1963

The Use of Strontium-85 in the Evaluation of Bone Metastases[1,2] A Preliminary Report

Sydney Kofman, M.D., Howard H. Sky-Peck, Ph.D., Yvian Thibaudeau, M.D., Robert D. Ray, M.D., and Samuel G. Taylor, III, M.D.

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"The skeleton is one of the most common sites of cancer metastases," and according to Jaffe (1) skeletal metastases are as common as pulmonary or hepatic involvement. Some common manifestations of osseous metastases are severe pain, collapsed vertebrae, pathological fractures, and hypercalcemia, which often lead to prolonged suffering and disability. Some of these complications, however, might be preventable by earlier diagnosis and treatment.

The principal method used to diagnose and to follow the course of osseous metastases has been by roentgenographic skeletal surveys. This method is crude, and a metastasis is not likely to be evident in the clinical roentgenograms until marked osteolysis or osteoplasia has taken place, or until the contour of the bone has been altered (2). Evaluation of the effects of therapy, as evidenced by recalcification of previously osteolytic lesions, is more difficult and usually requires a minimum of 2 to 3 months

In 1942 Treadwell (3) observed that strontium-89 accumulated in neoplastic osseous tissue. In 1959 Bauer and Wendenberg (4) showed that external counting of strontium-85 and calcium-47 could be of value in localizing skeletal lesions in man, and they noted that there was increased uptake of the isotope in regions of skeletal metastases. In a number of cases high isotopic uptake occurred where radiographic evidence was uncertain or not yet apparent.

The prime purpose of the present study, started in 1959, was to develop a simple and practical method that would be useful in early diagnosis and evaluation of therapy in patients with bone metastases.

---

[1]From the Departments of Medicine and Orthopedic Surgery, University of Illinois College of Medicine, and Presbyterian-St. Luke's Hospital, Chicago, Illinois.

[2]This project has been supported by grant C-5878 Rad. and grant CY-3060 of the National Institutes of Health, United States Public Health Service, Bethesda, Maryland.

METHODS AND MATERIAL

Four groups of patients have been studied:

1) Patients with known osseous metastases—9 patients.
2) Patients with suspect osseous metastases, but whose roentgenograms were either difficult to interpret or appeared normal—6 patients.
3) Patients with "normal" bones—6 patients.
4) Patients with nonmetastatic bone lesions (e.g., osteoarthritis, Marie-Strumpell arthritis)—3 patients.

A majority of the patients studied were out-patients; a few were hospitalized because of acute illness. The patients were re-examined at four week intervals or more frequently when indicated. In addition to routine histories and physicals, the patients had periodic chest x-rays, bone surveys, serum calcium, alkaline phosphatase, inorganic phosphorus, and liver function tests. These were usually repeated at intervals of three months or less.

At the onset of each study, 20 to 60 microcuries of strontium-85 were injected intravenously. External counts were made with a collimated 2 inch sodium iodide crystal. Pulses from the photomultiplier were amplified and then fed into a single channel pulse height analyser with a 7 volt window straddling the photopeak. The stability of the apparatus was checked frequently with strontium-85 and cesium-137 standards. Counts were made with the strontium standards

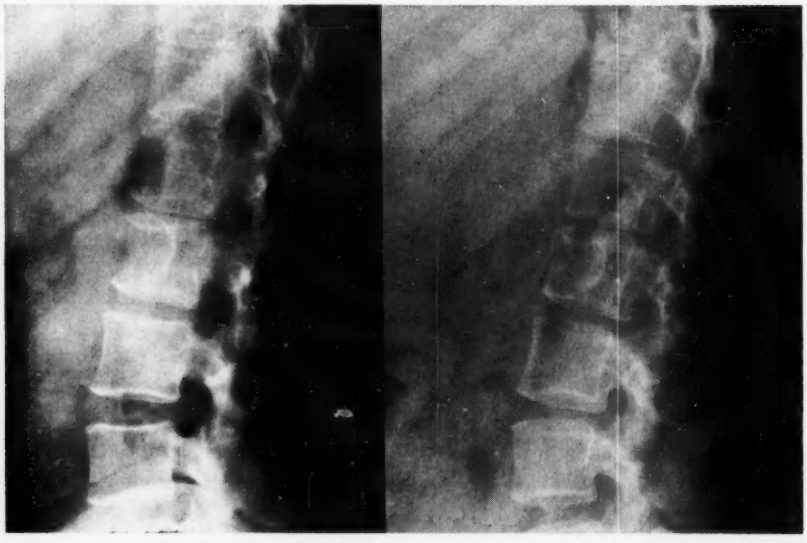

Figure 1. Metastatic lesion to lumbar vertebra before and after radiation therapy. Initial lesion was osteolytic and not detected by the vertebral scan. Subsequent roentgenogram revealed osteoblastic repair. At this time the metastasis was detected by the vertebral scan.

before and after each experiment. A minimum of 1000 counts was obtained over each area.

Mid-line bones (*e.g.*, vertebrae) were scanned at 3 centimeter intervals. Metal clips were used as markers, and roentgenograms were taken at the completion of the study. In the latter part of the study, blood samples were drawn during the middle of each experiment period, and counts were made on the plasma.

Repeat studies at short intervals were performed by scanning the vertebrae prior to the subsequent injections of strontium-85. These counts were used as background counts in the bones and were subtracted from the total counts. The repeat studies were performed when the counts had almost reached a plateau (usually one week or more after the initial injection).

The isotope studies were correlated with the clinical course, roentgenograms, and bone biopsies. In selected cases, the studies were performed before, during, and after therapy, which usually consisted of radiation or hormone therapy. The method used for the vertebral biopsies has been described by Ray (5). The roentgenograms were read independently by two radiologists, and the reports compared later.

ANALYSIS OF DATA

There are many ways that the data obtained from a vertebral scan can be analyzed. One simple method is to make ratios of the vertebral counts. Ratios were made in this study by using a vertebral count as the denominator and the subsequent vertebral count in descending order as the numerator. This method of analysis detected isolated vertebral metastases. However, "normal" ratios were often obtained in patients with diffuse vertebral metastases, since both counts used in the ratio were made over areas with skeletal metastases.

Three factors which are important in determining the uptake of strontium-85 by bone are 1) the dose injected, 2) the amount of isotope retained by the body, and 3) the metabolic activity of the bone. The first factor can be standardized by injecting the same dose or by expressing the counts as the number of vertebral counts per microcurie of strontium-85 injected. A pattern of scan was obtained by dividing each vertebral count by the number of microcuries of strontium-85 injected and plotting this value on linear graph paper opposite the vertebra counted. This "scanning pattern" was called "Pattern I." Comparisons could be made on several days in sequence following the injection.

"Pattern I," however, does not take into account differences in body retention of the isotope, and consequently, variations due to this factor (*e.g.*, in renal disease) might not be detected by this method of analysis. A second "pattern of scan" was obtained by dividing each vertebral count by the plasma isotope activity and plotting the values on linear graph paper opposite the vertebra counted. This "scanning pattern" was called "Pattern 2". Since both the uptake of strontium-85 into bone and the plasma isotope activity were related to the dose injected, this factor was cancelled out in the ratio.

RESULTS

To date 24 patients have been studied, and 6 repeat studies were carried out.

Eight out of the 9 patients with known metastases showed involvement by means of the vertebral scan. The vertebral scan was normal in the ninth patient. This patient had a large osteolytic lesion involving L2. The study was repeated several months later, following radiation therapy. At that time the lesion was smaller and showed osteoblastic repair by x-ray (Figure 1). It was detected on the vertebral scan.

Four of the 6 patients with suspected metastases had evidence of involvement by the vertebral scanning technique. When the roentgenograms were reread, the lesions were apparent in 3 patients and questionable in the fourth. The vertebral scans delineated the extent of involvement better than the roentgenographs in one of the 3 patients in whom the lesions were apparent on re-reading. The fifth and sixth patients had pain but no evidence of metastases on roentgenograms. The vertebral scans were normal. Subsequent long term follow-up revealed no evidence of vertebral metastases.

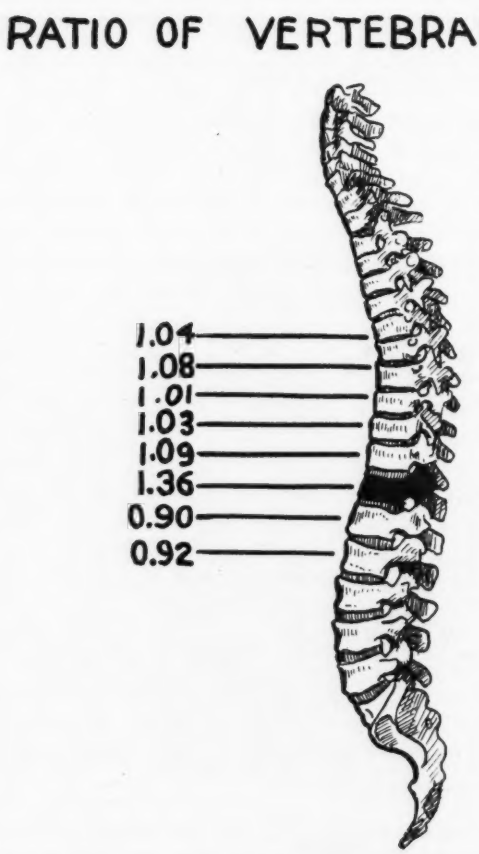

Figure 2. This illustrates ratios obtained by vertebral scan on the third day after Sr^{85} injection.

Six patients had "normal" vertebral scans, and follow-up studies revealed no evidence of metastases.

Two patients with hypertrophic arthritis had scans which resembled "normal" scans. One patient with rheumatoid spondylitis had a higher uptake of strontium-85 than "normal." This patient had ossification of the interspinous ligaments.

The ratios obtained in a patient with metastatic carcinoma of the breast involving a single vertebra are illustrated in Figure 2. The metastatic area is indicated in black. Reproducible ratios of 1.20 or greater were found to be significant in all cases. Metastases could usually be detected by the third day following the injection.

The mean vertebral counts per microcurie of strontium-85 injected, observed in 22 patients, are illustrated in Figure 3. The higher counts obtained over vertebrae with osteoblastic metastases were usually apparent by the third day following the injection. Patients with diffuse osteolytic metastases had counts near the upper limits of normal.

Figure 4 illustrates the "Pattern I" type of analysis on the third day following injection of strontium-85. The cross-hatched lines represent the distribution pattern in 5 patients without evidence of osseous metastases. Three patients with

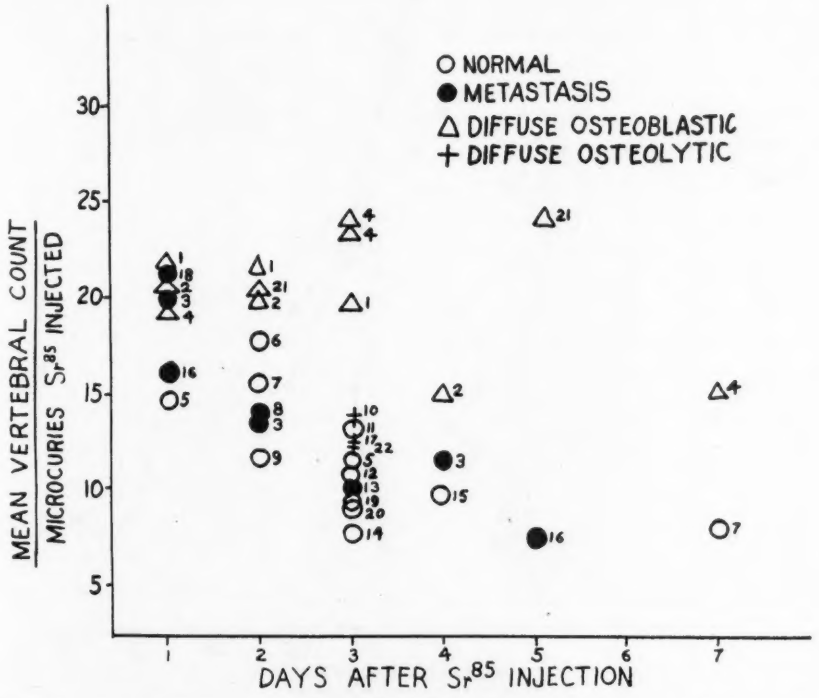

Figure 3. Illustrates the mean vertebral counts. Two values are given for Patient 4 on the third day after the injection of Sr^{85}. These studies were performed several months apart. No change in the clinical course was observed during this interval.

osteoblastic metastases had scan rates of strontium-85 which were 2 to 3 times that of "normal." The patients with diffuse osteolytic metastases had scan rates near the upper limits of normal.

Studies relating the vertebral counts to the plasma isotope activity were carried out in 11 patients ("Pattern 2" type of analysis). In these 11 patients the results were similar to those obtained with "Pattern I" in that the patients with osteoblastic metastases had uptakes of strontium-85 which were 2 to 3 times that of "normal," and the patients with diffuse osteolytic metastases had uptakes near the upper limits of normal.

One study was performed on a patient before and after bilateral oophorectomy. Prior to oophorectomy the "Pattern I" type of analysis suggested diffuse osteolytic metastases. Eight days following the oophorectomy the pattern was that of diffuse osteoblastic metastases in that the scan rate was much higher (Figure 5). Roentgenogram of the spine during the first study showed narrowing of the

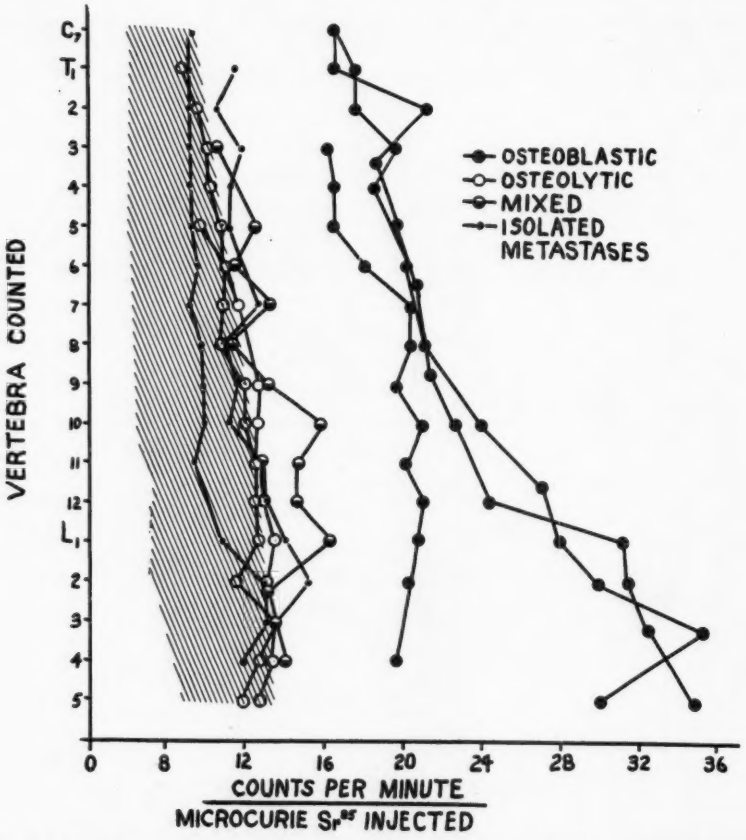

Figure 4. The "Pattern I" type of analysis is illustrated here. The increased uptake of Sr^{85} in patients with osteoblastic metastases is obvious.

4th thoracic vertebra, considerable destruction of the 12th thoracic vertebra with narrowing and areas of destruction in the 2nd and 3rd lumbar vertebrae. T4, T12, and L3 showed slightly higher counts than normal on the vertebral scan. Roentgenograms were repeated 2 months following bilateral oophorectomy. Views of the dorsal and lumbar spine showed a dramatic and diffuse increase in density when compared to the films at the time of oophorectomy. These findings were consistent with a regression of the metastases. A repeat scan at this time showed a scant rate similar to the scan rate 8 days following the bilateral oophorectomy.

DISCUSSION

The main purpose of this study was to develop a practical method for scan-

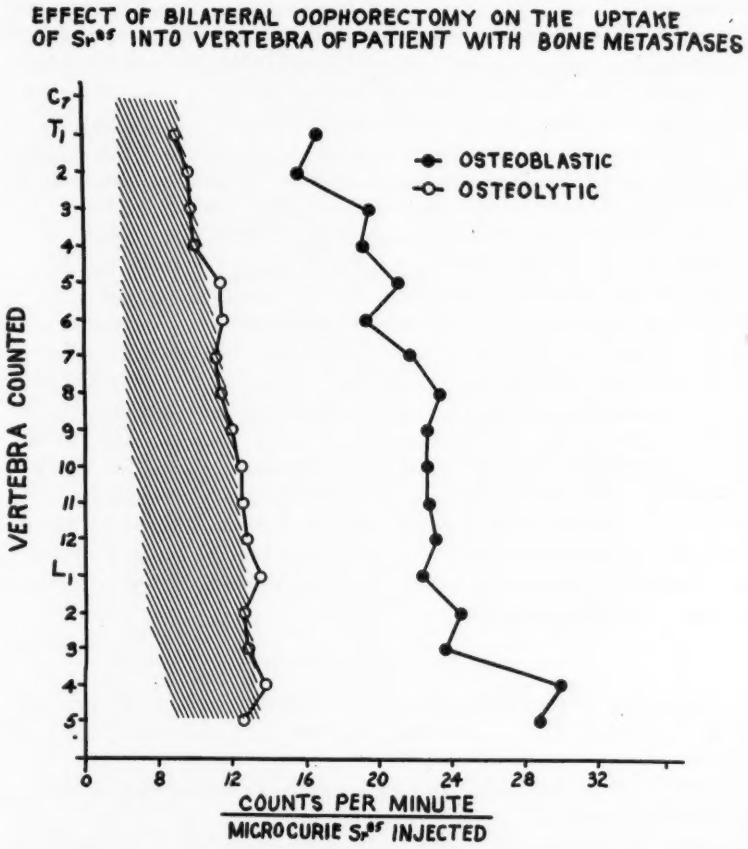

Figure 5. This illustrates the change in scan rate of Sr^{85} eight days following bilateral oophorectomy. The patient had a regression. Two months later the roentgenogram showed a marked increase in calcification of the metastatic lesions.

ning that could be useful in the early diagnosis and in the evaluation of therapy in patients with osseous metastases. Since the onset of this study, several reports have appeared in the literature confirming the value of strontium-85 and calcium-47 in detecting osseous metastases (6, 7, 8). Similar observations were made in this study, and a method for studying patients with diffuse vertebral metastases has been described. Using this method, patients with diffuse osteoblastic or "mixed" metastases can be readily differentiated from patients with diffuse osteolytic metastases and patients without osseous metastases—and changes in uptake of strontium-85 by the tumors as a result of therapy may be demonstrated within a few days.

The problem is much more difficult in patients with diffuse osteolytic metastases since the "patterns of scan" in some of these patients may closely resemble the patterns obtained in normal patients. In other patients with osteolytic metastases the uptake of strontium-85 is a little higher than normal. These observations made on patients with osteolytic metastases are not surprising when one considers the variation of metabolism in bone metastases. An increased uptake of strontium-85 in osteolytic metastases might be expected where there was coincident repair and destruction of bone. Failure to detect smaller osteolytic metastases may be due to the relatively crude resolution obtained with the detector used in this study. Improved delineation of metastases may be obtained by using a larger lens and better collimation. We are now using a 5 inch sodium iodide crystal with improved collimation which allows sharp delineation of metastases.

It has been emphasized that strontium-85 and calcium-47 can be used to detect metastases where radiographic evidence is uncertain or not yet apparent. There has been less emphasis on the observations that roentgenograms may reveal metastases where the uptakes of these radioactive isotopes are within normal limits. An additional problem encountered was that of interpretation of roentgenograms. Re-reading of roentgenograms revealed a greater tendency to under-read rather than over-read the roentgenograms. A similar problem related to the interpretation of miniature chest films has been discussed in detail by Garland (9).

There are now several methods available for studying patients with bone metastases:— 1) Roentgenograms, 2) Calcium balance studies, 3) Histological examination, 4) Autoradiographs, 5) "Accretion Studies", and 6) Scans. Each method studies a different aspect of bone metabolism, and each method has advantages as well as limitations.

SUMMARY AND CONCLUSIONS

1) A simple and practical method for scanning patients with vertebral metastases has been described. A vertebral scan from C7 to L5 can be done in 30 to 60 minutes.

2) This method is of value in studying patients with diffuse as well as isolated vertebral metastases.

3) Patients with mixed or osteoblastic metastases have a higher uptake of strontium-85 than "normals."

4) Patients with osteolytic metastases have "normal" or increased uptake of strontium-85.

5) Changes in uptake of strontium-85 as a result of therapy may be demonstrated within one to 2 weeks.

ACKNOWLEDGMENTS

We would like to thank Dr. Frank Hendrickson, Head of the Department of Radiotherapy, for his valuable assistance in setting up the study, and Miss Elda N. Metz for her technical assistance.

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Distribution of Radioisotopes in Tumors of The Rat Liver[1]

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INTRODUCTION

The study of liver lesions by external surveys of radioactivity has been of some clinical value and improvements in scanning equipment give promise of enhanced usefulness of such techniques. Investigators working with these techniques have not been able to detect small metastatic tumors in the liver, but major lesions or distortions of the shape or position of the organ have been clearly demonstrated.

Much of the work in this area has started with liver scans on patients, and a subsequent effort has been made to determine the degree of resolution and definition with which these scans indicate the actual distribution of the isotope in the liver. Opportunities to observe directly the state of the liver by surgical exploration or autopsy, and to compare this with the scan, are infrequent and may not occur until the disease process has been altered by time.

We have attempted to approach the problem from the other direction; that is to learn about the pattern of isotope distribution in experimental animals by autoradiography and radioassay with a view to selection of the optimal isotope preparation for scanning. Studies were done in rats, with the labeled compounds that are most commonly applied to clinical studies.

METHOD

Walker carcino-sarcoma 256 was grown in rats and suspensions of the tumor were prepared and strained through three layers of gauze. Male Sprague Dawley rats, weighing 150 to 300 g, were anesthetized with ether and nembutal (6 to 12 mg) and an abdominal incision was made. A 0.2 ml suspension of tumor cells was injected into the portal vein. After a period of 10 to 14 days the animals were again anesthesized and the radioactive material was administered through a tail vein. The isotopes used were iodine-131-labeled rose bengal, colloidal radiogold-198, and iodine-131-labeled human serum albumin. The sites of injection were

[1]From the Medical Division, Oak Ridge Institute of Nuclear Studies, Oak Ridge, Tennessee, under contract with the U. S. Atomic Energy Commission, and the Department of Surgery, University of Maryland, School of Medicine, Baltimore, Maryland.

checked by means of a radiation monitor for significant extravasation outside the vessel and those animals that had extravasation were eliminated from the study. For each radioisotope, groups of animals were sacrificed at 20 min and 24 hr after the injection of the radioactive material. The rats given rose bengal and radiogold were all subjected to perfusion with heparinized saline. The animals given iodine-labeled human serum albumin were divided into two groups—one perfused and one not perfused.

Approximately 100 animals were used to accumulate the data presented. The repeated anesthesia, operative procedures, and rapid progression of the tumor claimed a large percentage of the animals before they could be used successfully. Autopsy often revealed hemoperitoneum with peritoneal implants. In some animals the lesions in the liver were too small for adequate study; in others the liver was so completely replaced that no good comparison with normal liver tissue was possible. In some, no successful transplantation was obtained.

At the time of sacrifice the inferior vena cava and the aorta of the anesthetized animal were cannulated, and heparinized physiologic saline solution was injected into the vena cava as blood and perfusate were lost through the aorta. Cardiac arrest occurred within a few minutes after the beginning of the perfusion. In most animals the liver was obviously blanched by this time. Incomplete perfusion of the liver was recognized by the presence of dark areas usually at the periphery of the lobes.

Specimens of liver were obtained for gross autoradiograms and for radioassay. Tumor nodules were dissected from the normal liver, weighed in the fresh state, digested, and assayed for radioactivity. Similarly, areas of adequately perfused liver containing no gross tumor were also prepared for radioassay. The tissues containing gold-198 were digested with concentrated nitric and percholric acid (3:1), and those containing radioiodine were digested with 10 per cent sodium hydroxide. Since the information desired was the relative concentration of activity in tumor nodules and normal liver, and since specimens from the same animals were used for autoradiograms, no effort was made to determine the fate of all of the material injected and no corrections for physical decay were made.

Gross autoradiograms were prepared with Eastman Kodak no-screen X-ray film. Densitometer readings were made with a photovolt electronic densitometer Model 525 through a 1 mm aperture. It was not practical to obtain accurate measurements on the autoradiograms showing tumor nodules measuring less than 3 to 4 mm in diameter, and so larger examples were always chosen. In making the densitometer measurements on the autoradiograms, a straight line was arbitrarily drawn across the specimen in such a way that areas of normal liver and tumor would be included. (In the illustrations the extremes of these straight lines are marked by two dots.) The densitometer was then moved along these lines and recordings were made. In the illustrations the graphs were made by plotting the densitometer readings along the abscissa that corresponds to the distance across the specimen. Figures 1 through 5 show typical examples of results obtained; each figure is based upon one animal and shows a photograph of the liver (except Fig. 3), the autoradiogram marked with the extremes of the line of densitometer reading, and a graph of the densitometer readings.

Tables I, II, III and IV give the radioassay data and densitometer readings for an area of tumor and of normal liver in the different groups of animals. At

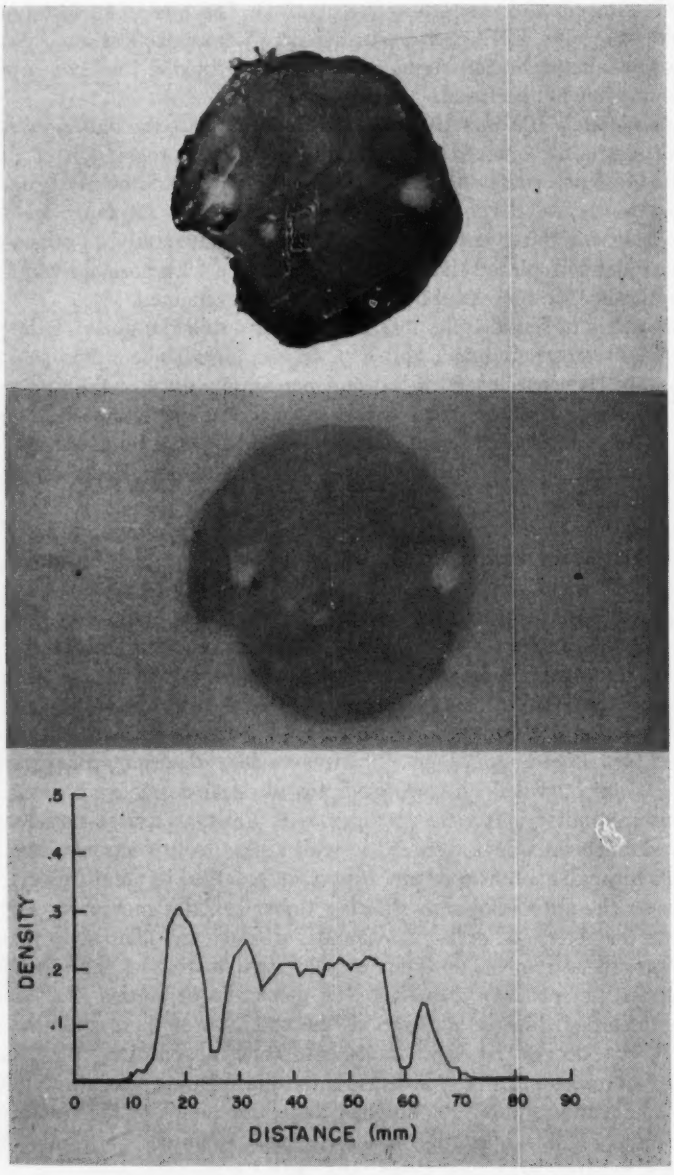

Fig. 1. Photograph, autoradiogram and densitometer scan of perfused tumor-bearing rat liver 24 hours after intravenous administration of Au^{198}.

those points in the tables where no figures are given for the densitometer measurements, the lesions were too small to make adequate readings of an area of tumor.

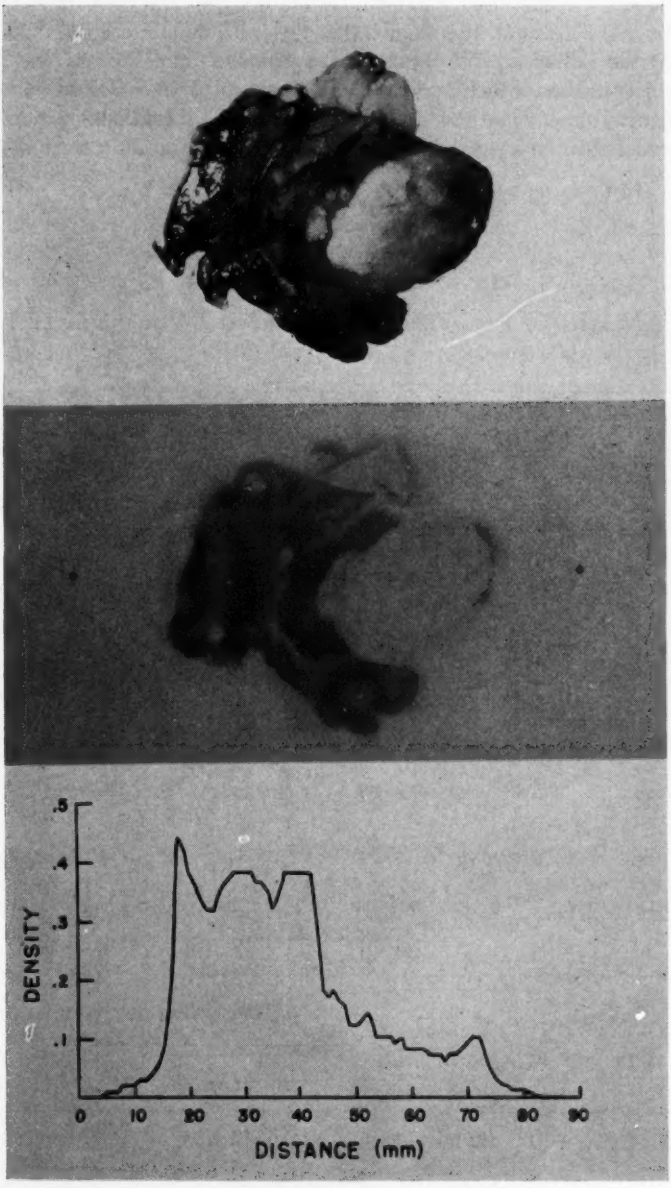

Fig. 2. Photograph, autoradiogram and densitometer scan of perfused tumor-bearing rat liver 24 hours after intravenous administration of rose bengal labeled with I^{131}.

RESULTS

Results show a wide variation in values for radioassay and densitometer measurements. On the other hand, the autoradiograms for each different isotope are reasonably consistent. It is known that the densitometer readings have limitations, but the radioassays of these small specimens of tissue are perhaps even more subject to inaccuracies, particularly because of smearing of radioactivity from adjacent areas when the specimens are cut. This contamination is particularly significant when a small mass of tumor containing no intrinsic activity is cut

TABLE I

CONCENTRATION OF COLLOIDAL Au^{198} IN NORMAL LIVER AND LIVER TUMOR (IN RATS)

Animal	*Time after injection*	*Ratio of liver concentration to tumor concentration*	
		By radioassay	*By ARG density*
1	20 min.	5.2	3.1
2	"	4.1	——
3	"	9.5	——
4	24 hr.	102.9	11.0
5	"	8.6	5.1
6	"	51.1	37.0

TABLE II

CONCENTRATION OF I^{131}-LABELED ROSE BENGAL IN NORMAL LIVER AND LIVER TUMOR (IN RATS)

Animal	*Time after injection*	*Ratio of liver concentration to tumor concentration*	
		By radioassay	*By ARG density*
7	20 min.	47.6	7.0
8	20 min.	6.7	——
9	24 hr.	3.6	4.0

from an area of relatively high concentration in normal liver. Falsely high values are obtained for the tumor specimen because of the contamination.

Autoradiograms—colloidal gold-198

The short term (20 min) and 24-hour intervals demonstrated essentially the same distribution. The areas of neoplasm showed little or no radioactivity, while in the normal liver tissue the gold-198 appeared to be rather evenly distributed. The normal liver did show a fine reticular pattern consistent with the distribution of Kupffer's cells.

TABLE III

CONCENTRATION OF I^{131}-LABELED HUMAN SERUM ALBUMIN (IN RATS—PERFUSED)

Animal	*Time after injection*	*Ratio of liver concentration to tumor concentration*	
		By radioassay	*By ARG density*
10	20 min.	2.0	—
11	"	0.6	—
12	"	0.8	—
13	"	0.6	0.5
14	24 hr.	0.8	0.5
15	"	0.8	0.2
16	"	0.3	0.3

TABLE IV

CONCENTRATION OF I^{131}-LABELED HUMAN SERUM ALBUMIN (IN RATS—NOT PERFUSED)

Animal	*Time after injection*	*Ratio of liver concentration to tumor concentration*	
		By radioassay	*By ARG density*
17	20 min.	2.7	3.3
18	"	1.7	—
19	"	1.0	—
20	24 hr.	11.8	—
21	"	0.6	—

Iodine-131-labeled rose bengal

Autoradiograms of liver obtained from animals sacrified 20 min after the isotope was injected showed a uniform distribution of radioactivity in the normal liver tissue. The tumor contained very small amounts of activity.

One animal was studied 24 hours after the isotope was given. Because of the expected rapid excretion, a large dose (500 microcuries) was used and the autoradiogram was exposed three times as long as for the short-interval animals. This study showed relatively more activity in the tumor, but much less than in the normal liver (Fig. 2).

Iodine-131-labeled human serum albumin

With perfusion at 20 minutes, in some animals the parenchyma of the normal liver tissue showed a distinct, uniform, fine mottled effect corresponding apparently to microscopic structure, but in others there was an irregular coarse mottling of uncertain significance. In some, an irregular dense band at the periphery suggested incomplete perfusion. The relative activity in areas of tumor was exceedingly variable and uneven within a given lesion. This activity ranged from concentrations well above to concentrations well below that of normal liver. Often the greatest activity was at the borders between the normal liver and tumor nodules.

Without perfusion at 20 minutes, the autoradiograms resembled those obtained after perfusion except that the peripheral zones of greater activity due to incomplete perfusion were not seen and there were no areas of tumor with more activity than the normal tissue.

With perfusion at 24 hours, the picture was not grossly different from the 20-minute perfused specimens, but no example was seen of the fine mottled pattern of normal liver. The tumor always appeared to have more activity than most areas of normal liver, but the contrast was not pronounced and the normal liver had a rather irregular concentration of activity.

Without perfusion at 24 hours, the results were quite variable. One example showed the fine anatomic pattern of the normal tissue while another showed a coarsely uneven distribution of activity in the normal liver. In both the autoradiograms showed the tumor to have little or no radioactivity.

DISCUSSION

The ideal radioisotope for locating a metastasis in the liver would be one concentrated in the neoplastic lesions at a much higher level than in surrounding liver. No isotope preparation that behaves in this way has been found. The hope that such a material may be developed is not great at this time; most elements and labeled compounds so far studied show a high concentration in normal liver tissue.

Although it is less satisfactory from a physical viewpoint to demonstrate an inactive area in a field of radioactivity, this is the best that is now available. Both

colloidal gold-198 and iodine-131-labeled rose bengal concentrate well in normal liver, with very slight amounts reaching tumor tissue. They are very different in their biologic pattern, the rose bengal passing rather rapidly through the biliary system to be excreted by the gastrointestinal tract (1, 2) while the colloidal gold-198 remains in reticuloendothelial tissue for a long period of time (3); simi-

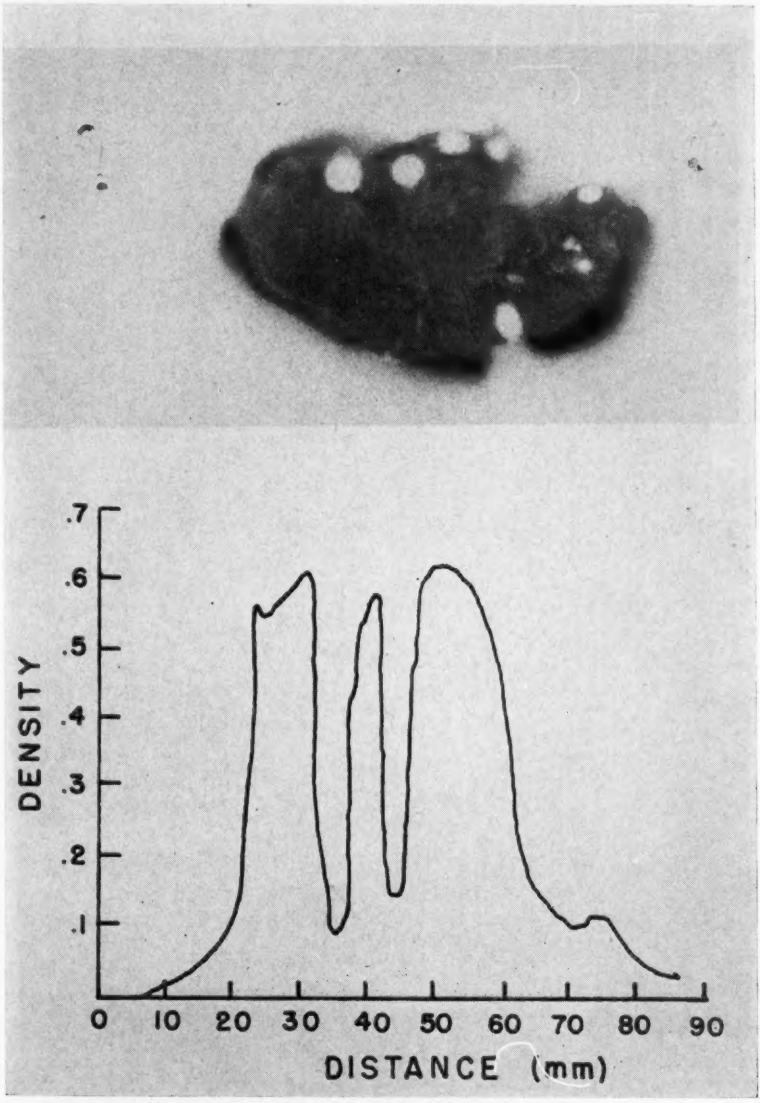

Fig. 3. Autoradiogram and densitometer scan of perfused tumor-bearing rat liver 25 minutes after intravenous administration of rose bengal labeled with I^{131}.

lar behavior is seen for other colloidal preparations as demonstrated in human patients (4).

For detecting neoplasms in the liver by scanning, the choice between iodine-

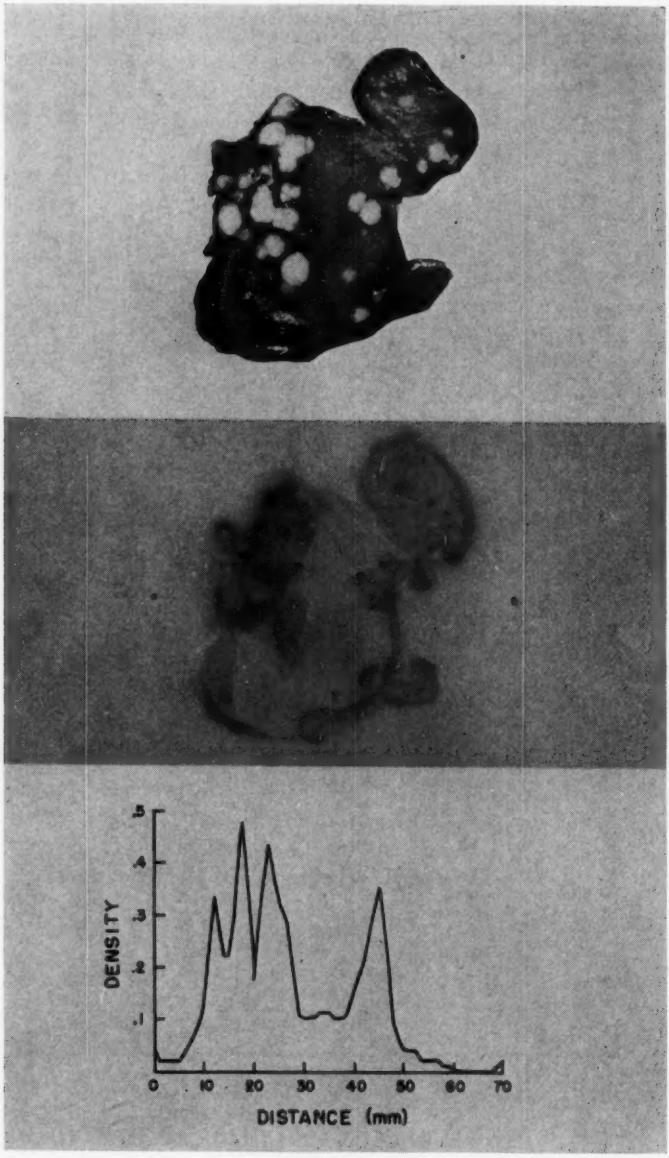

Fig. 4. Photograph, autoradiogram and densitometer scan of perfused tumor-bearing rat liver 24 hours after intravenous administration of human serum albumin labeled with I^{131}.

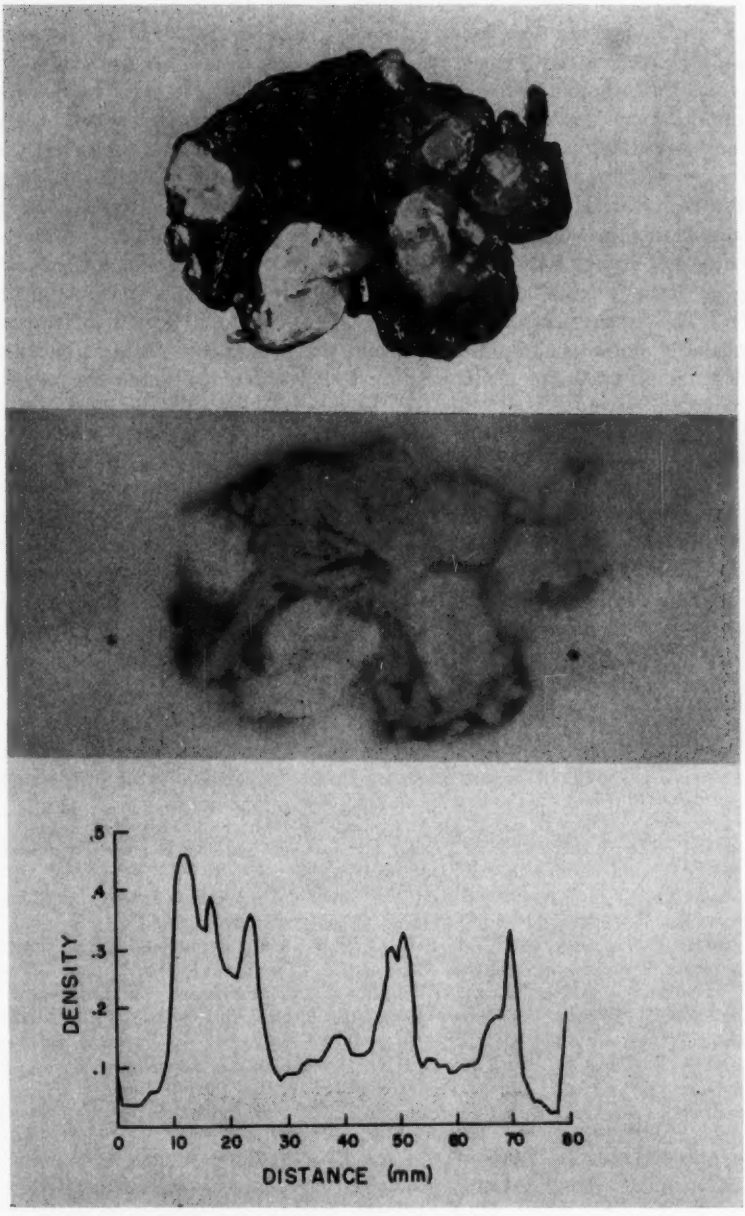

Fig. 5. Photograph, autoradiogram and densitometer scan of unperfused tumor-bearing rat liver 30 minutes after intravenous administration of human serum albumin labeled with I^{131}.

131-labeled rose bengal and colloidal gold-198 would seem to depend on radiation characteristics and the time factor in biologic behavior. Both isotopic preparations have a high concentration in normal liver tissue and negligible amounts in tumor.

Iodinated albumin presents a much more confusing picture. The distribution pattern in human and animal liver tumors is neither clear nor consistent, nor are the mechanisms understood (5, 6, 7, 8, 9). A previous study in rabbits (5) showed higher concentrations in tumor tissue. The present results may be influenced by the use of human albumin in rats and if mechanisms involving species specificity in albumin metabolism play a part, the results may be misleading. Still, the variable pattern of distribution of albumin in liver tumors, without clear contrast to surrounding liver tissue, is compatible with the confusing results reported in human studies. The mechanisms of distribution of the albumin may involve capillary permeability, intracellular utilization, and other unknown factors. The present study lends no encouragement to the use of iodinated albumin for location of liver tumors.

SUMMARY

1) In rats iodine-131-rose bengal and colloidal gold-198 given intravenously were distributed rather uniformly in liver parenchyma, and concentrations in tumors of the liver were exceedingly low.

2) Iodine-131-labeled human serum albumin showed inconsistent distribution in tumors of the rat liver.

ACKNOWLEDGMENT

Valuable assistance was given by Edgar Cress, John Rafter, and William Fishback.

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Absorption and Excretion of Radioactive Hg^{203} Mercaptomerin Sodium in Humans[1]

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In a previous publication, it was reported (1) that the parenteral administration of a single dose of Hg^{203} mercaptomerin sodium (N-(γ-carboxymethylmercaptomercuri-8-methoxy) propylcamphoramic acid disodium salt) into rats produced detectable radioactivity in plasma and renal tissue for 28 days. It thus appeared important to study the excretion pattern in man of Hg^{203} mercaptomerin sodium, and to compare it to that previously observed in rats. This is particularly important because mercurial diuretics are extensively used clinically and in the presence of renal failure a potential cumulative toxicity may be produced by retained mercury.

Hg^{203} mercaptomerin sodium was synthesized as described previously (1) and was characterized by chromatography, quantitative determination of Hg and S, temperature of decomposition and determination of diuretic activity. Solutions for injection were freshly prepared with pyrogen-free water, sterilized by filtering through a type H. A. millipore filter, and tested for sterility by incubating O.1 ml of the filtrate in sterile broth medium for 24 hours. The specific activity of Hg^{203} mercaptomerin sodium was 360 μc/mg mercury when assayed for gamma radiation. Single pharmacological doses were used which consisted of 250 mg mercaptomerin sodium, which is equivalent to 80 mg mercury, plus a trace dose of Hg^{203} mercaptomerin sodium. The radioactivity was adjusted so that each patient received only 15 μc per dose.

Radiopurity of Hg^{203} mercaptomerin sodium was ascertained by paper chromatography just prior to use. Four patients, 57 to 72 years of age, in right heart failure were treated in this study. Renal profile data for each patient was evaluated, and only one (A.L.) was found to have poor renal function. The mercaptomerin sodium with radiomercury was injected by the subcutaneous route. Venous blood samples were obtained periodically following drug administration. All patients were instructed to empty their bladders completely at each voiding. The urine collection periods did not necessarily correspond to the venipunctures. The

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sites of injection were monitored to determine time for complete absorption of radioactivity. After the plasma was separated from the red cells, paper electrophoresis was performed on the one hour sample to determine the plasma fraction to which the Hg^{203} was associated. This was done by cutting out from the electrophoretic pattern each protein fraction which was then placed in a well-counter to measure gamma radiation. All the samples of plasma and urine were assayed for radioactivity without any preparation other than dilution. All specimens were stored in tightly stoppered tubes to minimize errors due to mercury volatilization (2).

RESULTS

Blood: Figures 1 and 2 indicate that the plasma concentrations of radioactivity rose rapidly, reached the maximum between one and two hours, and then declined rapidly. The plateaus derived after three hours, represented 19 per cent of the maximum. The renal clearance of this substance rose slowly for the first two hours reaching the maximum within four hours.

Figure 3 illustrates the plasma concentrations in the presence of renal disease. In this instance, the concentrations of Hg^{203} attained a peak level of 2.5 times normal and was maintained over a four-hour period. Impaired renal function was also reflected in the renal clearance which, except for a slight peak at 0.5 hours was essentially level. Radioactivity in the plasma was detected for 168 hours after injection. In the presence of normal function, it was detected for only 48 hours. The electrophoretic studies revealed that the radioactivity was found only in the albumin and beta globulin fractions of the plasma.

Urine: The average amount of radiomercury recovered in the urine during the first four hours was 35 per cent and during the first 24 hours increased up to

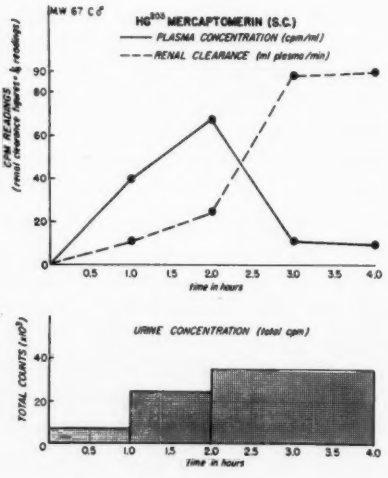

Fig. 1.

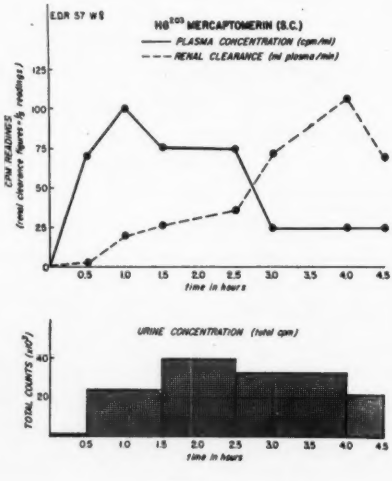

Fig. 2.

Figs. 1 and 2. Plasma and urinary excretion patterns in patients with normal renal function.

72 per cent. In the presence of renal failure, 18.4 per cent of Hg^{203} was recovered during the first four hours. Maximum concentrations followed peak plasma levels.

As can be seen, (Fig. 4) the highest concentration of radiomercury excretion (cpm/ml) occurred between 35 and 100 minutes and the maximum minute volume occurred between 175 and 280 minutes when the concentration of radiomercury excretion ranged between 90 and 100 cpm/ml.

Tissue: The average time required for complete absorption of radiomercury from the site of injection was 85 minutes by detection of radiation, whereas the absorption of mercaptomerin from an intramuscular site was found to be complete in approximately 60 minutes when estimated by chemical methods (3). The sensitivity of the radio-detection probably accounts for this difference.

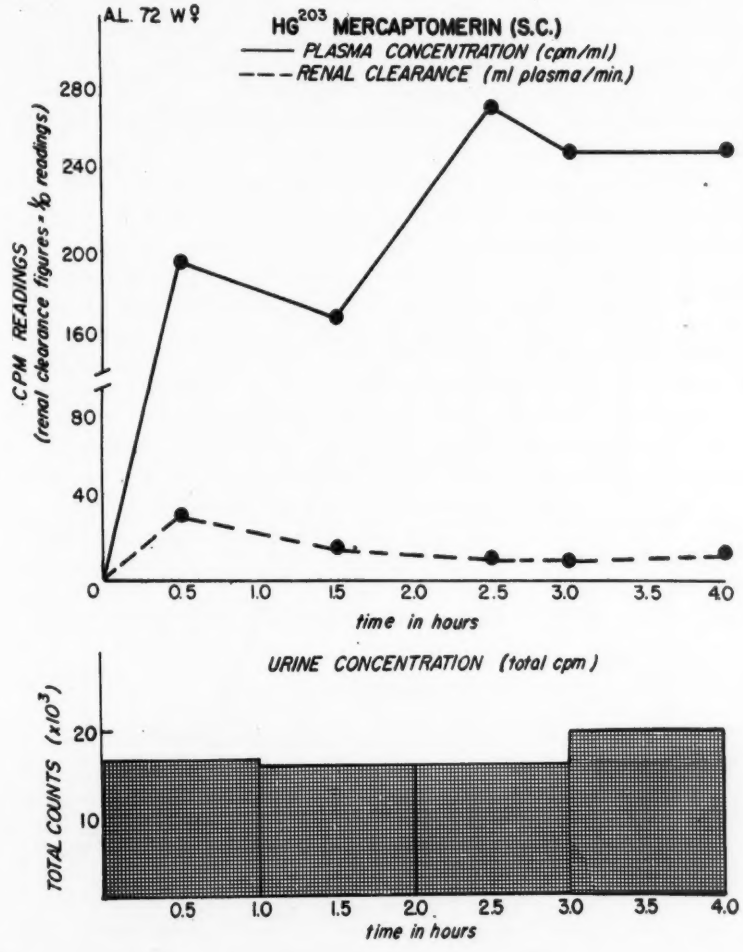

Fig. 3. Plasma and urinary excretion patterns in patient with poor renal function.

DISCUSSION

Mercury is protein-bound and stored in the renal parenchyma (4). Therefore, the term "renal clearance" requires a wide interpretation when used to study renal excretion with radiomercury. Since the biological decay of radiomercury in plasma parallels the concentration of radiomercury in the kidneys (1) the calculated renal clearance should reflect quantitative changes which may develop during experimental periods. Renal clearance of Hg^{203} reached a peak at approximately 240 minutes when both plasma and urinary concentrations were low, indicating that the plasma was cleared rapidly. This may be explained by the fact that mercury is rapidly taken up by renal cortex; whereupon, diuresis is initiated by a reduction of the functional capacity of the renal tubular transport mechanism. Therefore, some time is required to effect a maximum diuresis by possibly extending the number of functioning nephrons which become involved. The diuretic response depends not only on the presence of mercury within the renal tubules where it reversibly blocks certain enzyme systems, but also on the volume of extra- and intra-cellular fluid, electrolyte concentration, adequacy of glomeru-

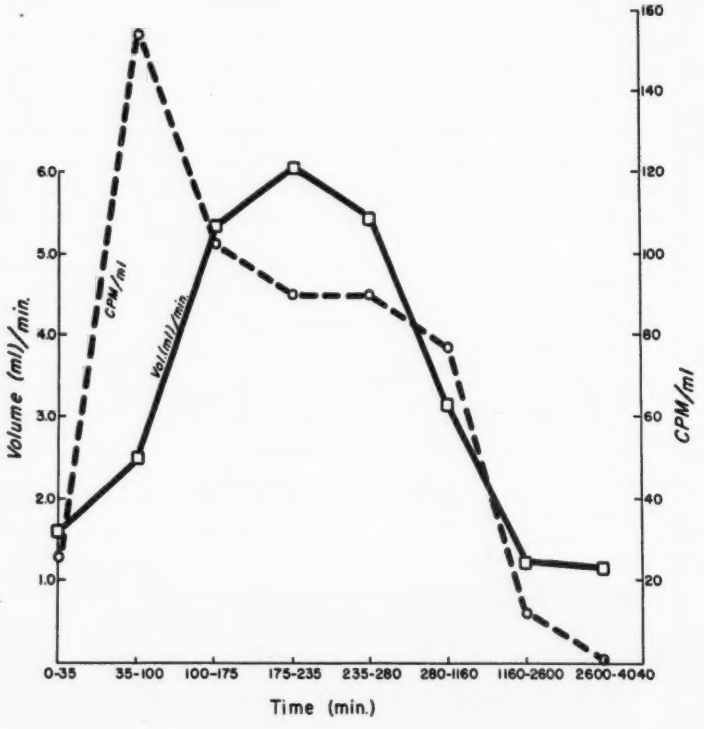

Fig. 4. Relationship between average minute urinary volume and average excretion (cpm/ml) of radiomercury following subcutaneous injection of Hg^{203} mercaptomerin sodium in patient without renal disease.

lar filtration, and hormonal balance. A critical concentration appears to be essential for maximum diuresis. That urinary excretion rate does not depend primarily on the rate of mercury excretion was suggested by observations that steroids altered electrolyte and water diuresis but not the rate of mercury excretion (6). The concept that a critical level of a mercurial diuretic is essential for maximum diuresis resulted from observations in animals (7). It was found that 4 mg Hg/kg produced the most effective diuresis in rats. Larger doses decreased diuresis; anuria with tubular damage resulted from doses of 12 mg Hg/kg.

The urinary recovery of radiomercury in this investigation is in agreement with the findings of others (8,3) who determined mercury by chemical analysis. On the other hand, similar results (5) were obtained using meralluride-containing radiomercury.

In the presence of renal disease, plasma concentrations remained elevated and signified a retention of radiomercury. This confirms human studies (5) and animal studies (9). A similar change in the biological decay of chlorothiazide was found in nephrectomized dogs (10).

The fact that radiomercury was found in plasma for 48 hours in patients with no renal disease, for seven days in the presence of renal disease emphasizes the need for caution in the administration of mercurial diuretics.

In the present investigation with Hg^{203} mercaptomerin sodium, the radiomercury measured total mercury and did not distinguish between the parent compound, metabolic products, and ionic mercury.

However, the unsolved problem as to whether it is the intact molecule or the liberation of mercuric ion has been suggested (11) that diuretic activity depends upon a specific molecular configuration with a "lock and key" relationship between the intact organic mercurial and receptor site. On the other hand, recent work (12) has demonstrated that all the organic mercurial diuretics are acid-labile in the presence of excess cysteine and the concept suggests that the mechanism of mercurial action involves the release of small amounts of mercuric ions which may occur at the site of action in the renal tubules.

Radioautographs of rat kidney following the administration of Hg^{203} mercaptomerin sodium (1) revealed similar localization to that obtained with radiomercuric chloride. The only valid conclusion to be drawn from these data is that mercury compounds, inorganic and organic, have similar histological sites of action.

CONCLUSIONS

Radioactivity was detected in the plasma for 48 hours when Hg^{203} mercaptomerin sodium was administered subcutaneously to patients in cardiac failure. In the presence of renal disease, it was detected in 7 days. Normally 72 per cent of the administered dose was recovered in the urine during the first 24 hours. A dissociated relationship exists between Hg^{203} excretion and the diuretic response.

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Announcement to Authors
Preliminary Notes

Space will be reserved in each issue of THE JOURNAL OF NUCLEAR MEDICINE for the publication of one preliminary note concerning new original work that is an important contribution in Nuclear Medicine.

Selection of the preliminary note shall be on a competitive basis for each issue. One will be selected after careful screening and review by the Editors. Those not selected will be returned immediately to the authors without criticism. Authors may resubmit a rejected or revised preliminary note for consideration for publication in a later issue. The subject material of all rejected manuscripts will be considered confidential.

The text of the manuscript should not exceed 1200 words. Either two illustrations, two tables, or one illustration and one table will be permitted. An additional 400 words of text may be substituted if no tables or illustrations are required. Only the minimum number of references should be cited.

Manuscripts should be mailed to the Editor, Dr. George E. Thoma, St. Louis University Hospital, 1325 South Grand Blvd., St. Louis 4, Missouri. They must be received before the first day of the month preceding the publication month of the next issue, e.g., preliminary notes to be considered for the March, 1963 issue must be in the hands of the Editor before February 1, 1963.

JOURNAL OF NUCLEAR MEDICINE 4:35-44, 1963

Scintillographic Follow-up of Amoebic Abscesses and Hydatid Cysts of the Liver[1]

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INTRODUCTION

We have performed hepatoscanning using intravenous injection of radioactive gold (1, 2, 3). The detection and spatial localization of deeply situated liver lesions have been performed according to our three plane hepato-scanning technique, the stereo-hepatoscanning, described previously (4) (Fig. 1, 2). By this method we have been able tc obtain additional findings to those detected by the classical AP technique in 46 per cent of the cases (5).

We have used stereohepatoscanning not only as a diagnostic tool, but also for the purpose of follow-up studies of liver lesions after treatment. In this way observations on the effects of internal and surgical therapeutical procedures could be followed. Special attention was paid in the present work to liver amoebic abscesses treated with emetine and with other antiamoebic drugs, and to the status of echinococcosis of the liver after surgical treatment.

METHOD

We used a sterile colloidal radioactive gold (Au^{198}) suspension received from Amersham, England, and injected it intravenously in a dose of 4-5 μc/kg of body weight. The scanning of the liver was begun 30 minutes after the injection, and performed by using a cliniscanner or an autoscanner with a multichannel focussing collimator and a Sodium Iodide crystal of 2 inches diameter, placed at 5 inches distance from the body. A survey of the anterior surface of the liver was performed, lateral and posterior examinations followed immediately. The whole procedure lasts about 1.5-2 hours. Radioactive Rose Bengal which is rapidly excreted into the bile (6) is not suitable for this type of scanning. Each hepatoscan was examined by two of us and evaluated by comparison with normal and pathological pictures, as established in a preliminary study.

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MATERIAL

The livers of 200 patients were examined, 48 of whom had parasitic diseases, 20 amoebiasis and 28 echinococcosis. The remainder were carcinomatous, cirrhotics, biliary cases, and normal ones, for control study. The data concerning sex, age, ethnic group and profession of the parasitic patients are summarized in Table I.

Half of them are current cases (7 amoebiasis and 17 echinococcosis) and the other 24 were follow-up cases, which had been treated 1-10 years previously (13 for amoebiasis and 11 for echinococcosis). The current cases were examined two, three and even four times: once before treatment and subsequently 2, 4, 6 weeks and 2-6 months after treatment. The follow-up cases were usually examined only once to establish their actual condition and the possibility of relapses.

Clinical, roentgenological, serological, parasitological and hematological examinations were carried out in all the cases. The laboratory and isotopic results were then checked by objective data obtained by post mortem examination, surgery, biopsy or results of therapy.

RESULTS AND COMMENTS

Among the 7 current cases of liver amoebiasis, 6 had abscesses and 1 presumably hepatitis. The scintilloscans of all abscess-cases presented one or more "Space Occupying Lesion" (SOL), which were exactly localized by the 3-plane-technique (Fig. 2). Following are details of two of them.

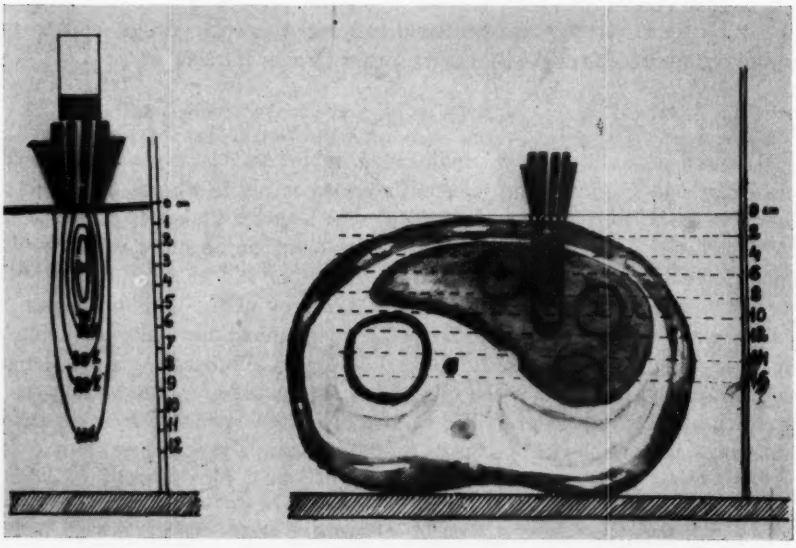

Fig. 1: Isoresponse curves of the multichannel focussing collimator. Their disposition into the liver during a classical AP hepatoscanning.

1) *Case C. A. No. 5070-47:* An amoebic liver abscess was established in the posterior-lateral part of the right lobe and confirmed by puncture and parasitological examination (Fig. 3a). 2 weeks after institution of emetine treatment, there were residual changes visible on the lateral scannogram (Fig. 3b,c). A third hepatoscannogram was completely normal one year after treatment. (Fig. 3d,e).
2) *Case W. L. No. 4931-19:* A large amoebic abscess was scannographed

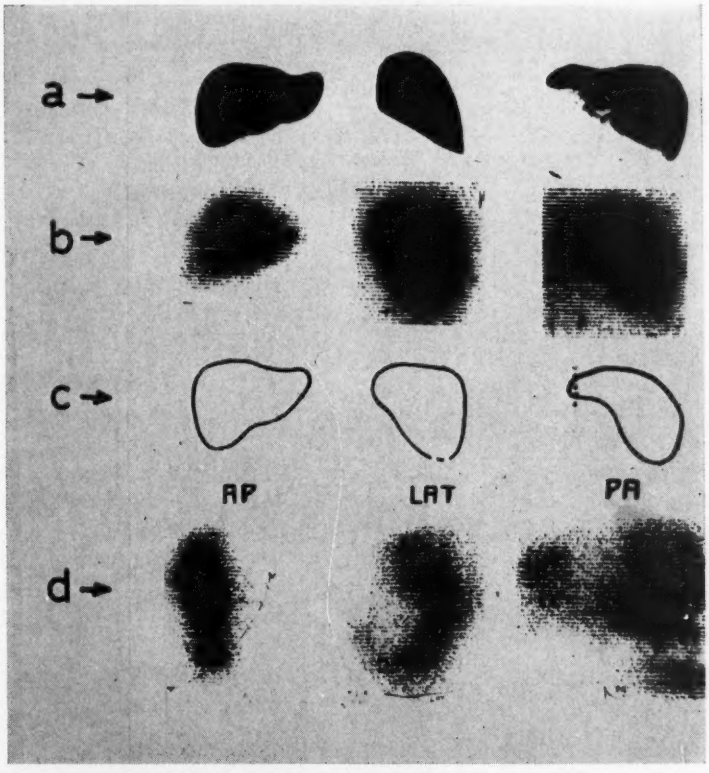

Fig. 2: The three plane hepatoscintillogram

a—the liver seen in AP, LAT and PA position

b—scintillograms of normal livers in AP, LAT and PA positions

c—schematic presentation of the normal liver scannographied in AP, LAT and PA position

d—Scintillograms of a pathological liver (echinococcus cysts)

***The AP scan:* A Space Occupying Lesion (SOL) in the left lobe is detected—the left lobe is not visualized.**

***The LAT scan:* A SOL in the posterior part of the right lobe is visible.**

***The PA scan:* The previously seen two SOL's plus a third one, paraverebral, are visible.**

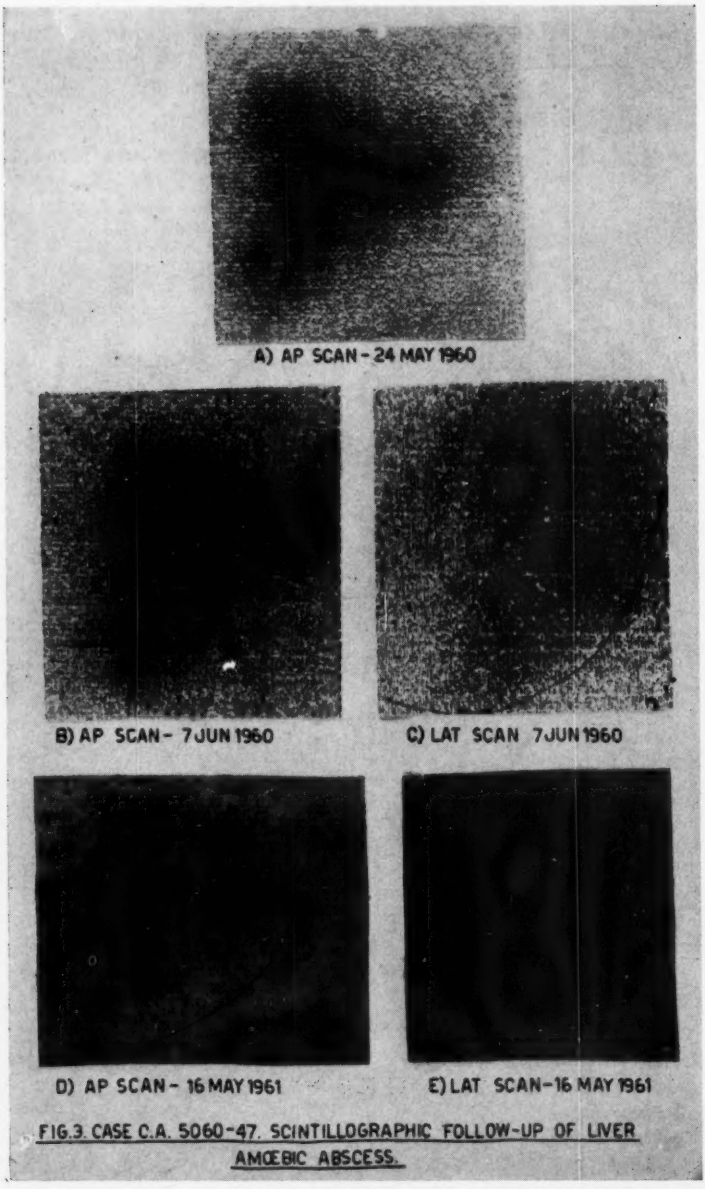
A) AP SCAN - 24 MAY 1960
B) AP SCAN - 7 JUN 1960
C) LAT SCAN 7 JUN 1960
D) AP SCAN - 16 MAY 1961
E) LAT SCAN - 16 MAY 1961
FIG.3 CASE C.A. 5060-47. SCINTILLOGRAPHIC FOLLOW-UP OF LIVER AMŒBIC ABSCESS.

Fig. 3: Follow-up study of a liver amoebic abscess. Liver scans before and after treatment.

in the right supero-posterior part of the liver (Fig. 4a). Two months after emetine treatment an almost normal liver scan was seen (Fig. 4b) and 6 months later the picture of the liver was completely normal (Fig. 4c).

In the case suspected for amoebic hepatitis (Case A. R. No. 5731-132) a "foggy" area in the interlobal region was detected, this area being clearer than the surroundings and not as homogenous (Fig. 5a). A rescanning performed 15 days later, after emetine treatment, showed an almost normal liver, coinciding with improvement of the clinical condition (Fig. 5b). The picture was completely normal 4 months later (Fig. 5c).

The 13 cases of amoebic liver abscesses, which were in the follow-up group, had been treated 1-4 years previously. The hepatoscintillograms now performed were normal in all but two. In one of them a Space Occupying Lesion was detected (relapse suspected), and in the other case the restitution was incomplete, as detected by a lateral scannogram of the liver.

In all 17 current cases of liver echinococcosis one or more SOL's were detected. The 3-plane scintillography localized the cyst topographically. These results were of help to the surgeons in their choice of approach in 15 operated cases (extirpation and marsupialisation). Following are details of two patients:

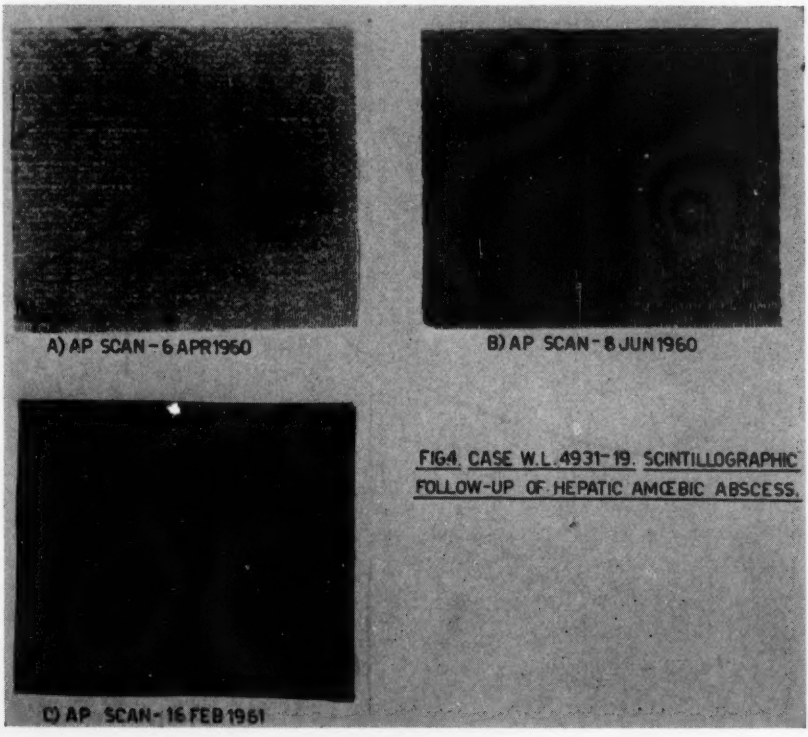
A) AP SCAN - 6 APR 1960
B) AP SCAN - 8 JUN 1960
C) AP SCAN - 16 FEB 1961
FIG 4. CASE W.L. 4931-19. SCINTILLOGRAPHIC FOLLOW-UP OF HEPATIC AMŒBIC ABSCESS.

Fig. 4: Follow-up study of a liver amoebic abscess.

1) *Case E. J. No. 5770-137:* was operated 5 years ago for hydatid cyst of the liver. The 3 scans of his liver show three round Space Occupying Lesions (Fig. 2d). The patient died 2 weeks later of a massive gastro-intestinal bleeding. On post mortem examination all of the 3 hydatid cysts were found in the situations shown by the hepatoscans. Moreover, a scar was detected in the left hepatic lobe, next to a cyst, this being the result of the previous echinococcectomy.

2) *Case B. C. No. 5175-68:* A round Space Occupying Lesion was localized by stereo-hepatoscanning in the retro-superior-right liver region (Fig. 6a,b,c). The AP scanning was almost normal, but the LAT and PA pictures were conclusive. The patient was operated by posterior approach and a rescannogram performed 10 months later shows the persistence of a non-restituted liver region, although smaller than the original SOL (Fig. 6d,e).

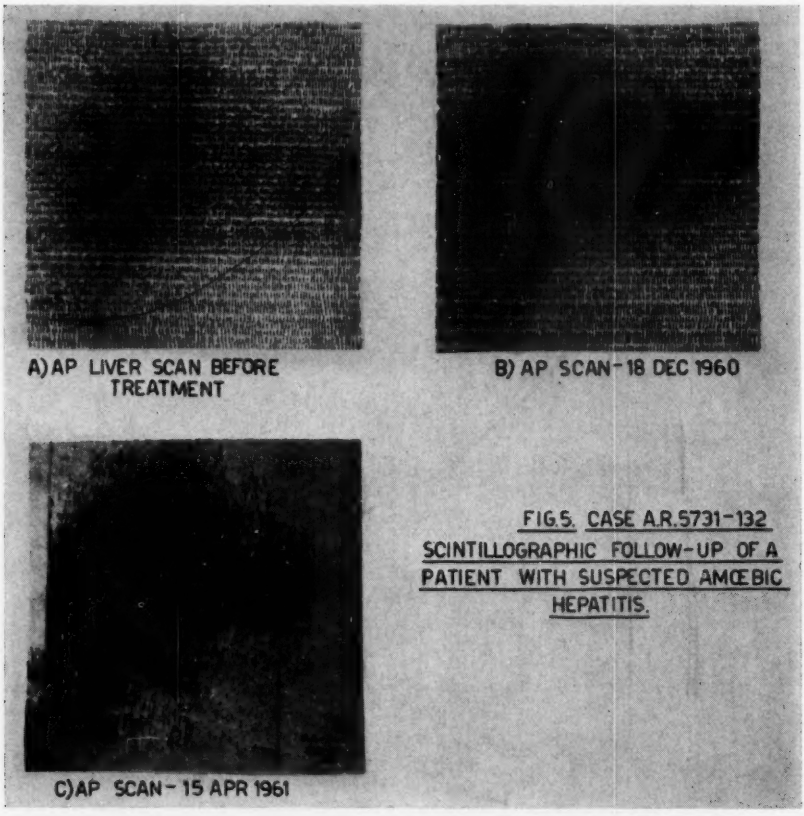
A) AP LIVER SCAN BEFORE TREATMENT
B) AP SCAN - 18 DEC 1960
C) AP SCAN - 15 APR 1961
FIG.5. CASE A.R.5731-132
SCINTILLOGRAPHIC FOLLOW-UP OF A PATIENT WITH SUSPECTED AMŒBIC HEPATITIS.

Fig. 5: Follow-up study of a case suspected for diffuse liver amoebiasis. Liver scans before and after emetine therapy.

Similar changes were found in all the other operated cases.

To complete the investigation we have performed scanning on 11 patients operated upon for liver hydatidosis from 1 to 10 years ago. In all but one, some

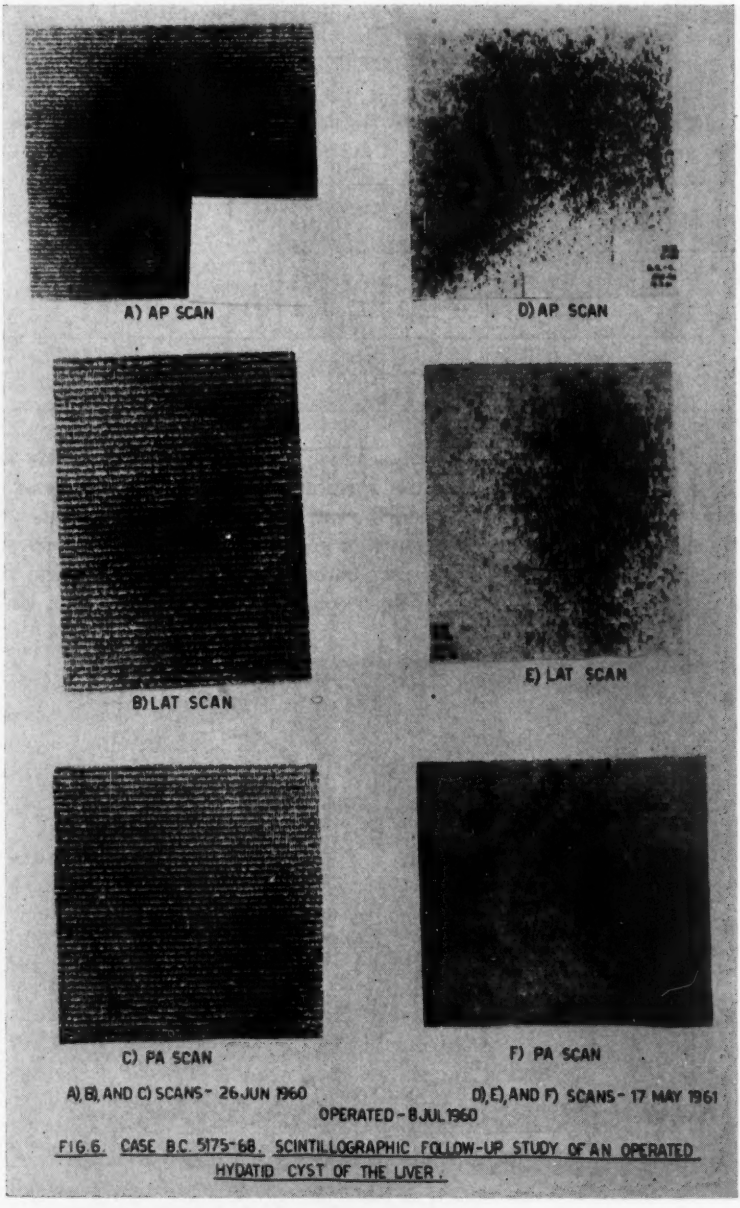
A) AP SCAN
D) AP SCAN
B) LAT SCAN
E) LAT SCAN
C) PA SCAN
F) PA SCAN
A), B), AND C) SCANS - 26 JUN 1960
D), E), AND F) SCANS - 17 MAY 1961
OPERATED - 8 JUL 1960
FIG. 6. CASE B.C. 5175-68. SCINTILLOGRAPHIC FOLLOW-UP STUDY OF AN OPERATED HYDATID CYST OF THE LIVER.

Fig. 6: Follow-up study of a hydatid cyst of the liver. Hepatoscans before and after operation.

TABLE I

LIVER AMOEBIASIS AND ECHINOCOCCOSIS

Diagnosis	*No. of pat.*	*Sex*		*Age*			*Ethnic group*				*Profession*			
		Male	*Female*	−30	−50	50+	*Ashkenazi*	*Sephardic*	*Yemenite*	*Arabic*	*House wife*	*Office worker*	*Farmer*	*Others*
Amoebiasis	20	15	5	4	13	3	10	8	2	–	3	3	3	11
Echino-coccosis	28	12	16	4	12	12	2	23	2	1	16	3	–	9
Total	48	27	21	8	25	15	12	31	4	1	19	6	3	20

abnormality was detected. The question always arises, whether there are recurrent cysts, or only fibrous scars of the operated ones. Fig. 7 shows 2 examples. In the first, a woman operated upon 6 years ago for an echinococcus of the antero-medial part of the liver, presents an encroachment in the scannogram. A relapse was suspected and she was reoperated. Thick, fibrous tissue was found in the place of her previous cyst. In the second case, an enormous cyst, situated

Fig. 7: Liver scannings of two previously operated livers for hydatidosis.

in the left hepatic lobe, was extirpated two years ago. No restitution is now visible; the right lobe is slightly hypetrophic.

For evaluation of our scannographic results we compare them with the results of other diagnostic procedures used for these liver diseases (Table II). It can be stated that positive scintillographic pictures were obtained in all confirmed cases of amoebic abscesses and liver echinococcosis. Cases of clinically suspected parasitic diseases of the liver, but with normal hepatoscans were followed up. Until now we have had not confirmation of the clinical suspicion nor negation of the scintillographic results. Some cases have been operated on for concurrent biliary tract disease and the liver has been found completely normal. On the other hand, roentgenological findings were nonspecific in the cases of amoebic abscesses and calcifications were found only in 7 of the 17 studied cases of hydatid cysts. Splenoportography (7, 8) is not included in the roentgenological procedures because it was not performed on our patients.

TABLE II

COMPARATIVE RESULTS OF 4 DIAGNOSTIC PROCEDURES

Diagnosis of the liver lesion	*No. of cases*	*Positive results in scanning examination*	*Roentgenological findings*			*Parasitological and serological findings*			*Confirmation of diagnosis*		
			Normal picture	*Indirect non-specific signs*	*Calcification*	*No findings*	*Suspected changes*	*Evident findings*	*Therapeutic test*	*Surgery*	*Pathology*
Amoebiasis	7	7	3	4	–	5	–	2	7	1	–
Echinococcosis	17	17	4	6	7	7	2	8	–	15	2

The results of serological, hematological and parasitological examinations were of lesser importance in the diagnosis of these two parasitic disorders of the liver, since positive or suspected results were obtained in 30-50 per cent of the cases only. The same evaluation of the results has recently been brought out by Birger (9).

CONCLUSIONS-SUMMARY

Stereohepatoscannography, using Au^{198}, was performed on 200 patients and special attention was paid to a group of 48 cases of amoebic abscesses and hydatid cysts of the liver. They were examined before and after treatment.

1) The diagnostic procedure shows a high degree of accuracy for these parasitic diseases, mainly for three reasons: the technique of 3-plane scanning, the collaboration with the clinicians, and the performance of additional examinations.

The positive and negative results of the three-plane hepatoscans were confirmed by objective data. The surgeons made use of the findings to select the approach and the clinicians to discuss their treatment.

2) The follow-up hepatoscanning study of liver amoebiasis and hydatidosis revealed:

a) Diffuse liver amoebic hepatitis is healed and the liver restituted 15 days after emetine-aralen treatment.
b) Amoebic liver abscesses shrink in size 2-4 weeks after emetine treatment, and filling of the Space Occupying Lesion by liver tissue is accomplished 2-4 months after treatment.
c) The liver regeneration after liver amoebiasis is almost always complete.
d) Operated liver echinococcus results in persistent deformity of the organ. This is most probably a fibrous, non-active scar, but the possibility of recurrence cannot be excluded.
e) The accurate interpretation of liver scannograms must be made in conjunction with anamnestic, clinical and laboratory data.

ACKNOWLEDGEMENT

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JOURNAL OF NUCLEAR MEDICINE 4:45-53, 1963

In Vitro Analysis of the Radioisotope Renogram Test[1]

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INTRODUCTION

The technique of radioactive renography, first described by Winter (1) and Taplin (2) use a dual system of a scintillation probe [-] rate meter [-] recorder arrangement to record independently for each side variations in count rate occurring over a kidney after an intravenous injection of a radioiodinated X-ray contrast medium. The recordings of these variations when obtained from normal individuals have the appearance of curves with distinct characteristics i.e., an ascending slope, a peak, and a descending slope (Fig. 1). The slopes have exponential characteristics and can be defined by the distance bo, which represents the time of the maximal count per minute; the distance Bb, which represents the maximal count per minute; and the distances oa and bd, which represent the half times of count increase and decrease. To facilitate the clinical interpretation of these recordings, it has become customary to divide the curves into three parts and to identify these parts with the vascular, tubular and excretory phase of elimination of the labeled compound by the kidney. We have reason to believe that this concept, as helpful as it may be for an understanding of renal physiology, has no application in the interpretation of the renogram curves.

It is the purpose of this study, first to find the physical factors that determine the profile of the renogram curve, secondly to analyze these factors for their effect upon that curve, and finally, to evaluate the results for their clinical significance. To this end we elected to use an in vitro method of analysis because it is faster, subject to better control, and more easily standardized.

MATERIALS AND METHODS

Figure 2 portrays diagrammatically the in vitro model. It consisted of an open ended series of tanks. Tank 1′ contained a volume V'_1 of enough water to

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last for the length of an experiment. Tank 1 contained a radioactive iodine solution of a known volume V_1 and a known concentration of 0.025 millicuries/V_1. Tank 2 contained water of a known volume V_2. The solution was propelled through the system by the force of gravity at a constant and equal rate, while V_1 and V_2 were maintained. The radioactivity in tank 2 was monitored by one of the two renogram units, consisting of a scintillation detector, a rate meter and a recorder. The settings of these instruments were identical to the settings used in the clinical tests. There was one inch of water between the detector and tank 2, mimicking the absorbing tissue between kidney and detector. The degree of reproducibility of this technique is illustrated in Fig. 3, which shows two recordings obtained at different times but under identical conditions.

This in vitro model permitted us to change at will the values of its three principal components: the volume in tank 1 (V_1), the volume in tank 2 (V_2), and the rate of flow of solution into and out of tank 2 (F). Starting arbitrarily

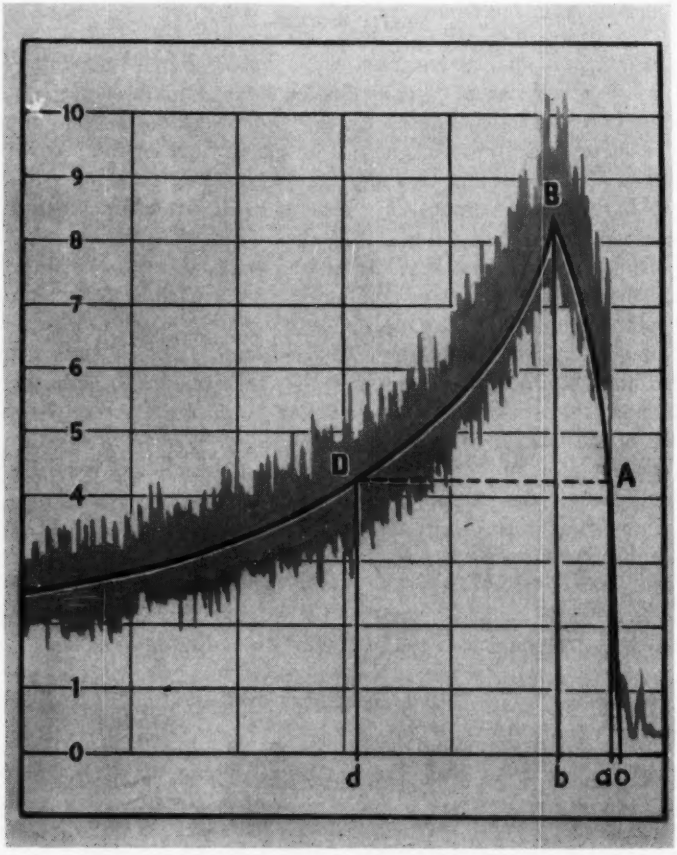

Fig. 1. "Normal" renogram curve with analytical measurements superimposed. bB = maximal count; bo = time of maximal count; oa = half time of count increase; bd = half time of count decrease.

with V_1 and V_2 measuring 250 cc each and with a flow rate of 16 cc per minute, we varied the values, one at the time, by a factor of 2 and made a total of 12 runs with 6 different combinations of V_1 and V_2:

V_1	250	250	125	125	62.5	62.5	cc
V_2	250	125	125	62.5	125	62.5	cc

Each one of these 6 combinations was run twice at different flow rates, once at a flow rate of 8 cc and once at a flow rate of 16 cc per minute.

RESULTS

The recordings obtained from these 12 experiments differed distinctly from each other but they all had the following characteristics in common: the exponential rise and decline of count rate and the point of maximal count rate of varying height, occurring at varying times; in other words, the curves had the basic characteristics of a renogram curve. In addition we found that one of the 12 tracings had a close resemblance to the curves obtained in a study of 9 normal individuals, for whom tracing B in Fig. 4 was representative (3). Tracing A in this figure represents the in vitro curve, for which V_1 was 62.5 cc, V_2 62.5 cc, and F 16 cc per minute.

The comparison of the 12 in vitro curves with each other afforded us the opportunity to make some interesting observations. By comparing two curves, differing only in one of the three components at the time we could study the

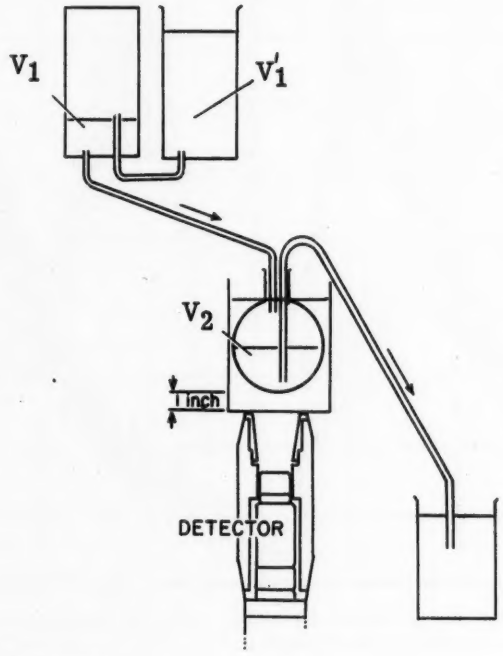

Fig. 2. In vitro model; see text.

effect of these components on the curve. Fig. 5 shows a selection of such comparisons. The top part of it shows the effect of an increase in V_1: the curve flattens, and the maximal count (bB in Fig. 1) decreases; on the other hand an increase of V_2, shown in the bottom part of Figure 5 increases the maximal count. In both cases, however, the time at which the maximal count occurs (ob in figure 1) is very little effected, while it definitely is effected by a change in flow rate as shown in the middle part of Figure 5: an increase in flow rate decreases the time of maximal count and vice versa. Thus, it seems that V_1, V_2, and F are principle factors responsible for the shape of the curve.

DISCUSSION

In the design of our in vitro model we were guided by the intention to mimick as closely as possible the in vivo conditions. Our primary concern was to build a structure that would represent the kidney. Careful considerations of all the facts led us to assume that the kidney, although anatomically as well as physiologically a complex system of compartments, the principal ones of which are the tubular and the vascular space, represents with regard to the renogram technique a single compartment, comparable to a tank with water of a certain

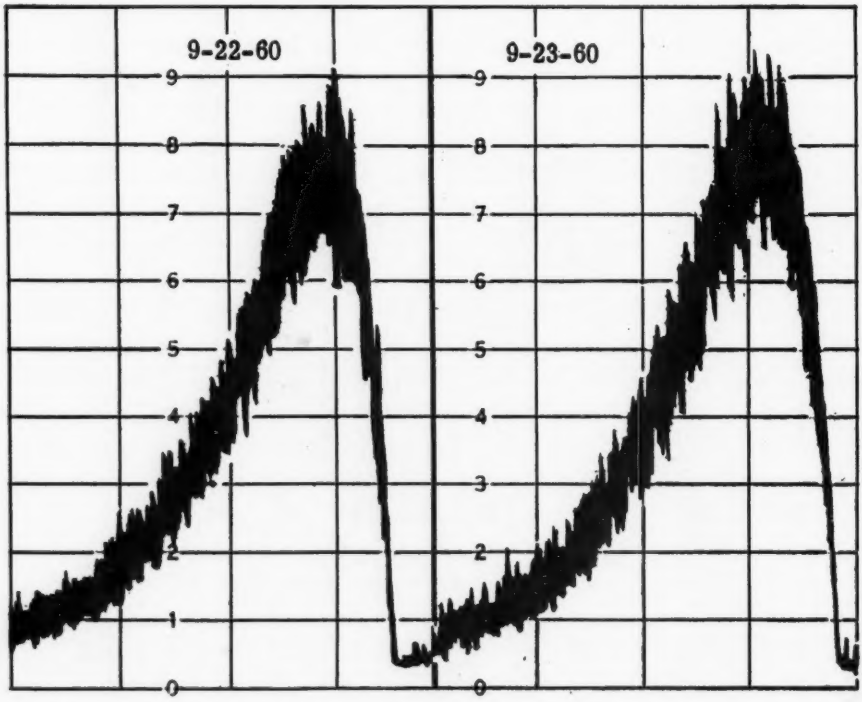

Fig. 3. Two tracings obtained at different times under identical conditions; to show the degree of reproducibility of the technique.

volume, such as tank 2 in our model. We arrived at this assumption by the following thoughts: A renogram curve as a recording of count rate fluctuations in the visual field of the detector probe represents radioactivity of changing concentration in the renal tissue included in this visual field. Figure 6 is a schematic drawing of the renal constituents seen by a properly placed detector. Any radioactivity, entering through the renal arteries, passing through the glomeruli, secreted into the tubules and collected in the collecting system and renal pelvis will be recorded for its presence and strength, no matter where in the system it is at the time and thus the structures through which the labeled compound passes is comparable to a one-compartment pool, as is tank 2 in our model with regard to the renogram record. If, on the other hand, a radioisotope solution is passed through a tank with a constant volume of water, radioactivity accumulates until the loss of activity is in equilibrium to the gain. The recording of such an event, we know, produces a curve which rises to the point of equilibrium from where on it runs horizontally as long as radioisotope solution flows into the tank at the same rate at which it leaves the tank. The factors that make the curve fall after the point of equilibrium are to be sought in a progressive dilution of the inflowing radioisotope solution, an effect, we attempted to produce by the arrangement of V_1 and V'_1 in our model (Fig. 2), where the high initial concentration, leaving

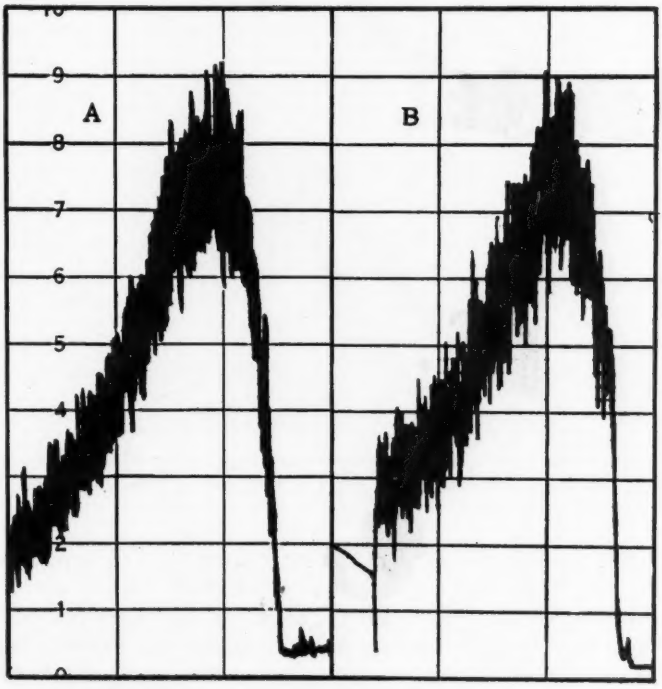

Fig. 4. Tracing A is an in vitro curve, tracing B is a renogram curve from a study of 9 "normals"; to show the comparability of the in vitro model with the in vivo conditions.

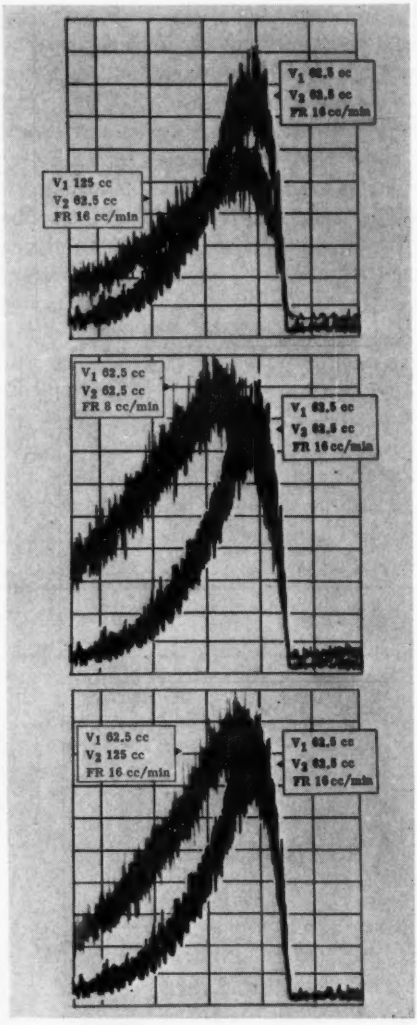

Fig. 5. Comparison of in vitro curves, obtained from experiments with differing values for V_1, V_2, and F; to demonstrate the effect of each one of these factors on the curve; see text.

V_1 is constantly decreased by dilutent flowing in from V'_1. This approximates the in vivo situation because as one injects a radioisotope solution into a patient intravenously, this solution will be diluted at first in only a fraction of the total blood volume. Consequently, the radioisotope solution will arrive at the kidney level as a bolus of a certain size and concentration. This bolus of radioactivity is constantly diluted by recirculation as well as renal excretion of the labeled compound.

For these assumptions there is no other readily available proof but the experiment, which does suggest by the close resemblance of the experimental curves with the in vivo curve (as shown in Fig. 4) that the assumptions are correct. Further support for this conclusion comes from the fact that V_2 of tracing A in Fig. 4 was 62.5 cc which is comparable to the size of the tubular space of a human kidney which can be assumed to be approximately 63 cc, because the tubular space of a 20 kilogram dog was calculated with 18 cc by stop flow analysis. In addition, we compared our results with the results obtained by Veall and Vetter (4). They found in their experimental work of radioisotope exchange between compartments, done by sampling, that in an open two-compartment system, as it applies to our model, the relation between the concentration in tank 2 at any given time and V_1 and V_2 and flow rate can be expressed in the following equation:

$$C_2 = C' \left(\frac{V_2}{V_1 - V_2}\right) \left(e^{-Ft/V_1} - e^{-Ft/V_2}\right)$$

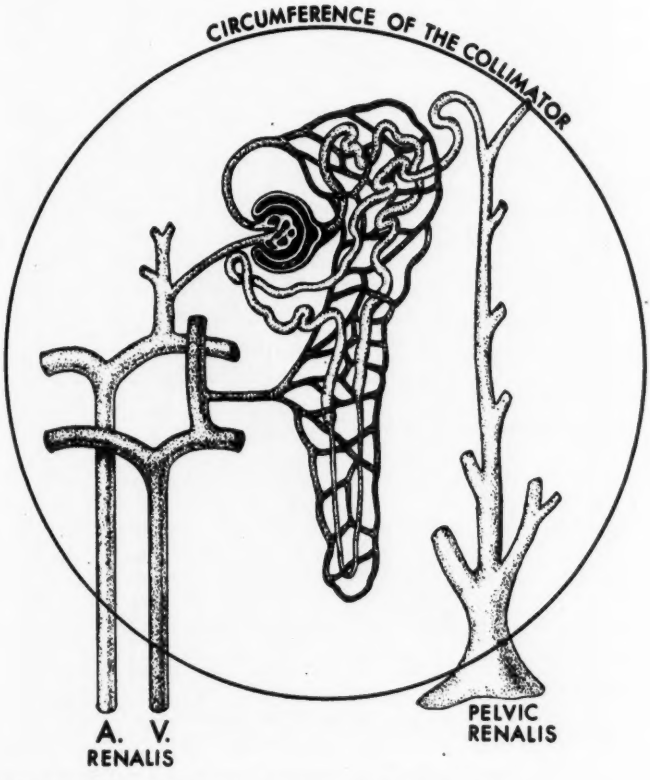

Fig. 6. "Field of vision", of the detector in a renogram test; see text.

where V_1 is the fluid volume in tank 1, V_2 is the fluid volume in tank 2; C′ is the initial concentration in V_1; C_2 is the concentration in V_2 at time t; and F is the flow rate of fluid between the tanks. When we substituted the values from our model in this equation, we found that the agreement between our in vitro model and their mathematical model was not perfect but adequate to prove the comparability of the two. The degree of agreement is demonstrated graphically in Fig. 7.

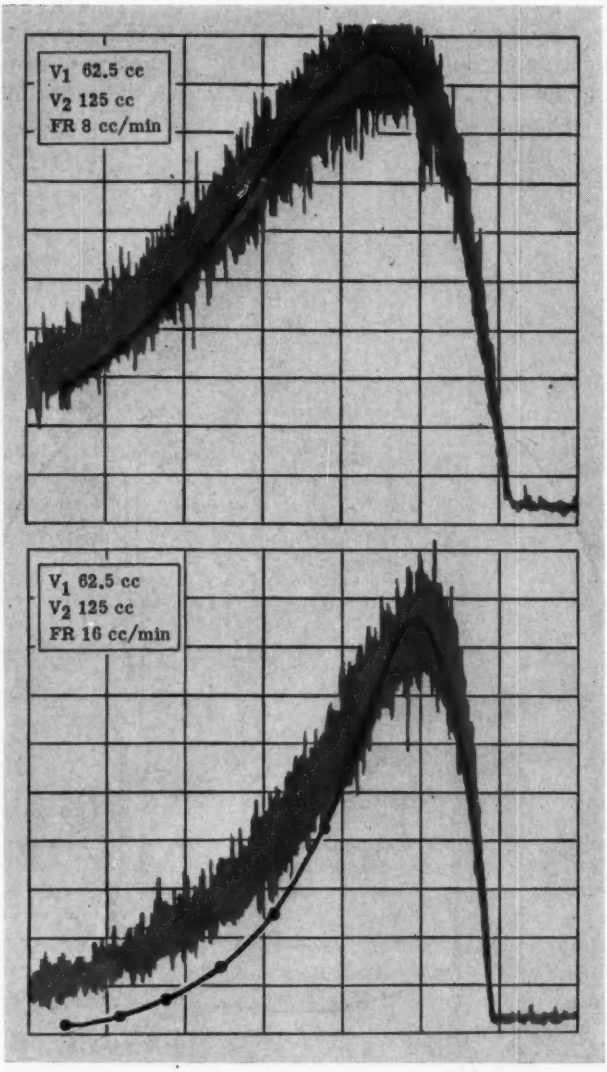

Fig. 7. In vitro tracings (grey) with values calculated from Veall's mathematical model superimposed (—•—); to demonstrate its applicability to the in vitro model.

SUMMARY

An attempt was made to analyze the radioisotope renogram curve by an in vitro method, using the model of an open two-compartment system. The factor V_1 and V'_1 of this system was assumed to be comparable to blood volume, V_2 to functional volume of the kidney, and F to arterial blood flow to the kidney. The results indicate that these three factors are responsible for the shape of the renogram curve. The most influential of the three appears to be the renal blood flow, which has a pronounced inverse effect on the time of maximal count, while the functional volume of the kidney and the blood volume effect the maximal count but not the time of maximal count, at least not appreciably.

Naturally these conclusions must be treated cautionusly because of the risk that one takes when mimicking physiological conditions with simple models. The results at their best can't be more than an approximation of the true state of affairs. However, it appears to us that the results of this study will at least be helpful to the interpretor of renogram curves. Furthermore, it seems justified to conclude that the results obtained by the method of external counting, when performed skillfully, are not equal, but comparable, to the results obtained by the method of sampling.

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A Simple Device for Milking High-Purity Yttrium^{90} from Strontium^{90} [1,2]

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INTRODUCTION

Yttrium-90 is a radioisotope that has attracted favorable attention over the past few years because of its potentialities as a radiotherapeutic agent. It has been used as a source of intense local radiation in systemic, intracavitary, and interstitial applications (1). It has a half-life of 64 hours, emits a single beta of 2.27-Mev maximum energy, and has no gamma radiation associated with it. It decays to stable Zr^{90}.

Yttrium-90 may be readily produced by two different methods. One is the (n, γ) reaction on natural yttrium (100% Y^{89}), using thermal neutrons in a nuclear reactor. This method requires very pure Y_2O_3 for the target material, to minimize the production of extraneous long-lived gamma-emitting activities. The product Y^{90} is not carrier-free, which may be a disadvantage in some applications, and the short half-life requires careful scheduling of irradiation and use if much of the activity is not to be lost by decay, increasing its cost appreciably.

Since Y^{90} is formed by the decay of a long-lived parent, 28-year Sr^{90}, it may also be obtained by separating or "milking" it periodically from its parent activity. Figure I shows the growth and milking of Y^{90} graphically. Over a period of two weeks, for example, Y^{90} grows in until it reaches 98 per cent of its equilibrium value. In 24 hours it reaches 23 per cent of equilibrium. Thus it is possible to milk over 20 mC of Y^{90} daily from a 100-mC Sr^{90} source. Such a source provides a convenient way of obtaining Y^{90} for clinical use. This method has the advantages of "on-the-shelf" availability, low-cost, and a carrier-free product. Its one disadvantage lies in the extreme toxicity of the parent Sr^{90}. Two microcuries of Sr^{90} fixed in bone is the current lifetime maximum permissible dose (2). It is therefore essential that both patients and handling personnel be protected against

[1]This work was performed under the auspices of the U. S. Atomic Energy Commission.

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ingestion of any Sr^{90}. The means employed to milk Y^{90} from Sr^{90} must give a completely clean separation, consistently and reliably, so that there will be a minimum of residual Sr^{90} in the Y^{90} product. Several methods have been devised for separating Y^{90} from Sr^{90} and some of these give an Y^{90} product relatively free from Sr^{90}. However, these methods tend to be complex, and may involve considerable hazard when quantities of the order of hundreds of millicuries of Sr^{90} are being handled. Other methods give products that are contaminated with too high a level of Sr^{90} to permit their use on humans.

The Y^{90} generator or "cow" developed at Brookhaven National Laboratory provides a simple, rapid, and safe means of effecting this separation. The extremely low Sr^{90} content of the product solution permits its general use without special precautions. This Sr^{90} contamination is only a factor of 10 or so higher than the 8×10^{-7} μC/cc that is considered permissible for continuous lifetime ingestion in drinking water (2). The generator is designed to be used in the conventional clinical radioisotope laboratory, and its operation requires no specialized training or technique.

DESCRIPTION AND OPERATION

The Brookhaven Y^{90} generator, Figure 2, employs a column of Dowex-50 x 8 cation exchange resin contained in a glass column about 1½ inches in diameter

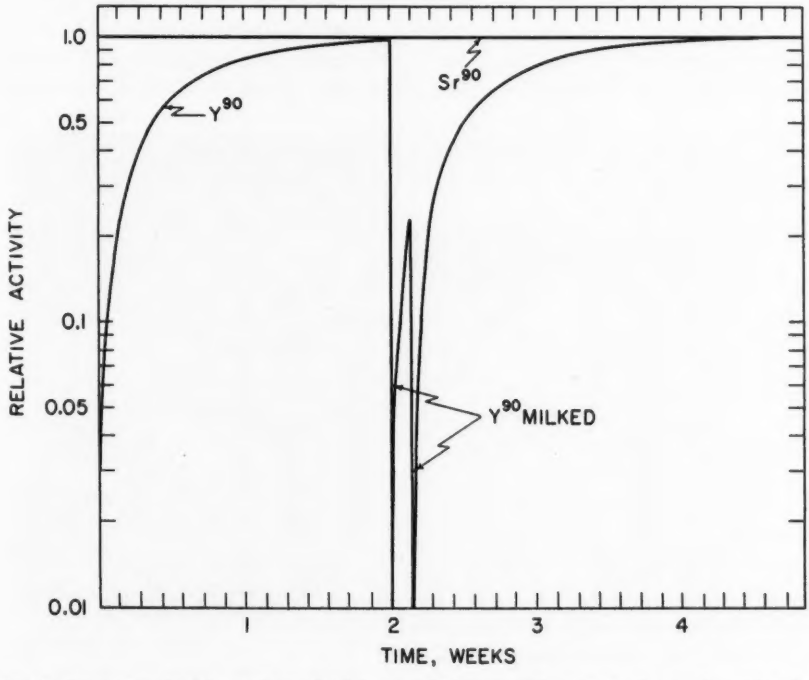

Fig. 1. Curve showing the milking of Y^{90} from Sr^{90} after growth periods of 2 weeks and 1 day.

and 7 inches high to effect the separation of Y^{90} from Sr^{90}. The Sr^{90} is fixed on resin in the upper part of the column. This resin is retained at the top of the column by glass filter-cloth supports. It is thus prevented from mixing with the bulk of the resin in the lower part of the column as the result of shock or vibration during shipping or handling. Any Sr^{90} that may leak off the resin in the upper compartment, as the result of radiation damage for example, will be caught by the resin below.

The glass column is mounted in a plastic cylinder 4¼ inches in diameter and 13 inches high. This cylinder protects the glassware against breakage and would contain the resin should breakage occur. It also serves as a beta radiation shield. The radiation level is approximately 50 mr/hr at the outer surface of this cylinder and less than 1 mr/hr at 3 feet from it, when 100 mC of equilibrium Sr^{90}-Y^{90} are on the column.

The generator is ready for use as it is received. To operate it, first a rotary slide is moved, causing the product delivery tube to emerge from the plastic housing. This delivery tube is retracted into the housing during shipping or storage, to prevent breakage. The stopcock, near the base, is turned to the open position and 100 ml of eluting solution are poured into the reservoir at the top of the generator, through a funnel set in the inlet port. The eluting solution is a 0.5% citric acid solution whose pH has been adjusted to 5.50 with ammonium hydroxide. As this solution passes down through the column, Y^{90} that has grown in is complexed by the citrate ion and is stripped from the resin. The Sr^{90} is unaffected and remains behind. The product solution is caught, in a 100-ml flask, as it emerges from the delivery tube. The dimensions of the generator are such

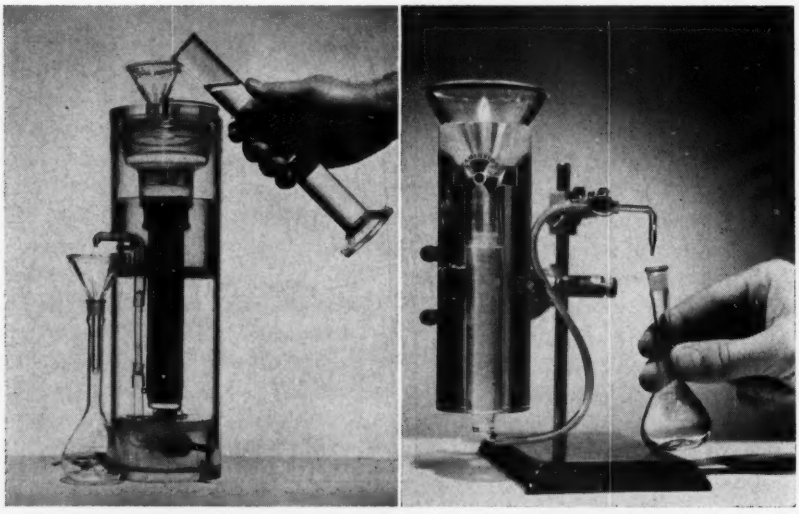

Fig. 2. Operation of the Brookhaven Y^{90} generator.

Fig. 3. Column used in assaying Y^{90} for Sr^{90} contamination.

that with 100 ml of solution in the reservoir, the flow rate through the column is very close to the optimum 4 ml/min. As the solution level drops in the reservoir, the flow rate decreases slowly until it is down to about 3 ml/min at the end. A milking thus takes about ½ hour. At the bottom of the reservoir is a small bed of powered alumina, retained by a glass frit. The eluting solution passes through this bed as it leaves the reservoir. When the level of the solution drops to the surface of the alumina, the flow of product solution out of the delivery tube stops abruptly. There is thus no dripping from the nozzle, no danger of the receiving flask overflowing, or of the liquid level dropping below the top of the resin bed and the resin drying out. Once the reservoir has been filled and the stopcock turned on, the generator requires no further attention until after the milking has been completed.

A yield of 98 per cent of the Y^{90} present at time of milking is obtained. The Sr^{90} contamination in the product solution is less than 0.001 μC per 100 ml of product solution, or, for a 100-mC Y^{90} milking, the ratio of Sr^{90} to Y^{90} is less than 10^{-8}.

The Y^{90} as it comes from the generator is carrier-free. There is an excess of citrate ion associated with it. For some physiological applications it may not be desirable to have the yttrium in the form of a citrate complex. However, this complex can easily be broken in any one of several ways. Yttrium hydroxide may be precipitated by a strong NaOH solution, after the addition of yttrium carrier, or the Y^{90} may be obtained carrier-free by co-precipitating it with ferric hydroxide. It may also be separated from the citrate ion on a small column of cation exchange resin, the Y^{90} being eluted carrier-free with hydrochloric acid. Alternatively, the citrate ion may be destroyed by taking the product solution nearly to dryness after addition of 30 per cent hydrogen peroxide or of a mixture of nitric and sulfuric acids.

ASSAYING FOR SR^{90} CONTAMINATION

The experience over the past four years at Brookhaven and in the field with generators loaded with 100 mC of Sr^{90} each has been uniformly good with respect to both the high yield of Y^{90} and the low level of Sr^{90} in the product solution. Since no milking has been found to contain appreciably more Sr^{90} than expected, a considerable degree of confidence in the generator has been built up. However, for Y^{90} that is to be administered to patients it is necessary to be able to show that the Sr^{90} content of any given batch is well below the level where any hazard exists. Conventional methods of radioanalysis are too slow, too complex, or too insensitive to be of use in this application. To check on the Sr^{90} contamination level as well as to guard against a gross contamination of the product solution as the result of an accident or maloperation of the generator, an assay method was developed that would satisfy the requirements (3). It will detect as little as 0.02 μC of Sr^{90} in the presence of 100 mC of Y^{90}. It takes about 1 hour to perform and uses a small aliquot of the product solution, so that each milking may be tested before administration. In this way there can be confidence on the part of laboratory personnel in the purity of the Y^{90} being handled and a protec-

tion against both the real and the psychological hazards of working with Sr^{90}. While the method will not detect the extremely low levels of Sr^{90} normally present, it will detect an increase in this level by a factor of about 20. This is still well below the point where any hazard would exist.

The assay method employs a small column of Dowex 1 x 10 anion exchange resin in the bicarbonate form, Figure 3. The column, with its beta shield, and a supply of resin accompany each generator. A 5-ml aliquot of the product solution is taken and 1 ml of a carrier solution, also supplied, containing 3.5 mg of yttrium and 0.2 mg of strontium is added. This solution is washed through the assay column with sufficient 0.001 *M* ammonia to give a total effluent of 25 ml. In passing through the resin bed, the yttrium is retained as a citrate complex by the anion exchanger while the strontium is unaffected. A decontamination factor of about 10^7 is obtained with respect to Y^{90} and over 90 per cent of the Sr^{90} passes through. An aliquot of the effluent is evaporated on a planchet and counted in an endwindow beta counter, with and without an aluminum absorber of about 220 mg/cm^2 interposed. This absorber is thick enough to remove completely the Sr^{90} beta (0.54 Mev), while allowing part of the harder beta from the small Y^{90} residue to pass through. To compute the amount of Sr^{90} present, the count through the absorber is corrected for partial absorption of the Y^{90} beta by application of a previously determined factor, and the corrected count is subtracted from the bare count. The difference is the count attributable to the Sr^{90} present.

AVAILABILITY AND SERVICE LIFE

The Brookhaven Y^{90} generator is currently available to laboratories holding the requisite AEC license for the possession and use of Y^{90} and Sr^{90} in the desired quantities (4).

During the development of the generator, it was found that the level of the Sr^{90} contamination in the product solution rose slowly with time, increasing by about a factor of 100 over a 2-year period. While the Sr^{90} content is still quite low, less than 0.001 μC per ml, generators are being limited to a use period of one year and a loading of 100 mC. At the end of one year they are returned to Brookhaven for disposal. The reason for the slow increase in the contamination level appears to be radiation damage to the resin, it being a function of the amount of activity on the column and of the length of time that the column has been loaded. It does not seem to be affected by the number of milkings made or the total volume of eluting solution passed through the generator. As more experience is gained with the behavior of the generators in operation under a variety of field conditions, the use period and the amount of Sr^{90} loaded on a generator may be increased. Over the course of a year, it is possible to milk 5 Curies of Y^{90} from a 100-mC generator, assuming daily milkings over a 5-day work week. Even if only a fraction of this activity is used, Y^{90} becomes one of the cheapest isotopes available.

The generator was made available for general use in the latter part of 1960, after the satisfactory completion of a 5-month field test at the Medical Division of the Oak Ridge Institute of Nuclear Studies.

SUMMARY

The Brookhaven Y^{90} generator makes Y^{90} readily available at low cost to radioisotope laboratories anywhere for research and clinical applications. Tests over a period of four years have demonstrated its reliability in supplying Y^{90} in high yield, with a Sr^{90} contamination consistently below 10^{-5} μC per ml. The simplicity of the generator's design and operation and the check on the radiopurity of the product solution provided by the rapid Sr^{90} assay make for a high degree of safety in its use.

ACKNOWLEDGMENT

We wish to thank Dr. Granville C. Kyker, Chief of Preclinical Research at the Oak Ridge Institute of Nuclear Studies' Medical Division, for undertaking the field-testing of the Y^{90} generator, and for his subsequent comments and suggestions.

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Determination of Total Body Water With Tritium Oxide (H_2^3O)[1]

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INTRODUCTION

The determination of total body water has always been difficult. In the early 1950's, the Atomic Energy Commission released Tritium (H^3) for metabolic studies. We became interested in its use for total body water determination for the following reasons: it was inexpensive, rapid, accurate, simple and most important, very safe.

This study was carried out in a group of 200 patients selected as relatively healthy subjects free of significant metabolic derangements. Most were patients admitted for minor elective surgery or diagnostic surveys. One hundred patients were males and 100 were females. Ten patients of each sex were selected to represent each decade of life from birth to senescence.

MATERIAL AND METHODS

The apparatus used in this study was a fast coincidence liquid scintillation counter (Tri-Carb).[2] The photomultiplier tubes were encased in lead shields and housed in a deep freeze unit at a temperature of 0-8°C. Counting efficiency varied between 6 and 9 per cent. Background was never above 40 cpm.

The scintillation solution was prepared according to the method of Langhan[1] as follows: 7 gm. of 2,5-diphenyloxazole (PPO); 50 gm of naphthalene and 50 mgm of 1,4, -bis-2(5-phenyloxazolyl) benzene (POPOP) made up to one liter with p-dioxane (analytical grade). Dark adaptation was not necessary for this procedure.

Injection: A stock solution of 2 mc/cc of tritium oxide delivered as sterile distilled water was made and stored under sterile conditions. This was used for

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[2]Packard Instrument Co., Inc., La Grange, Illinois.

the adult doses. For young children a dilution to give 1 mc/cc was used, and for infants and newborns 0.1 mc was used. In each the total quantity was 1 cc. Delivery was with a Cornwall springe previously calibrated to deliver 1 cc with an accuracy of 0.003 per cent.

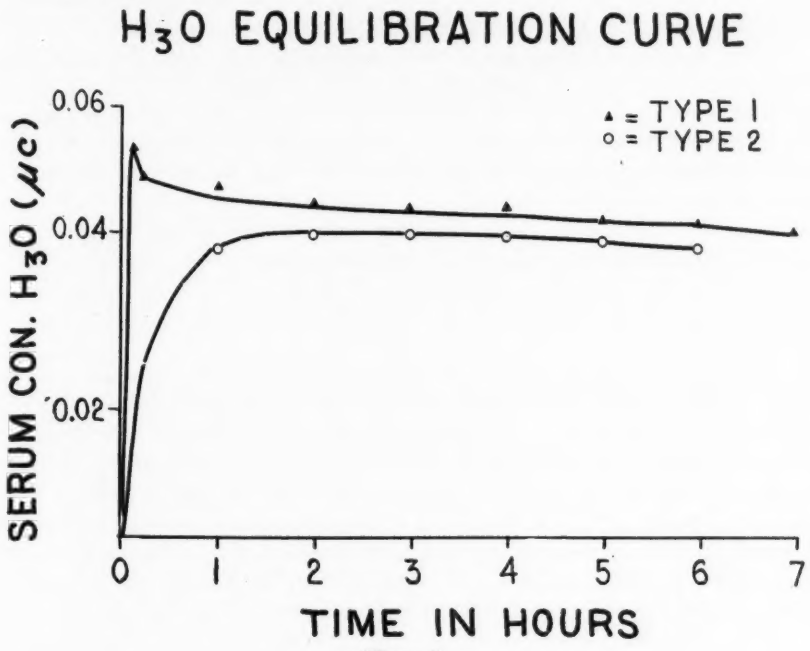

Figure 1.

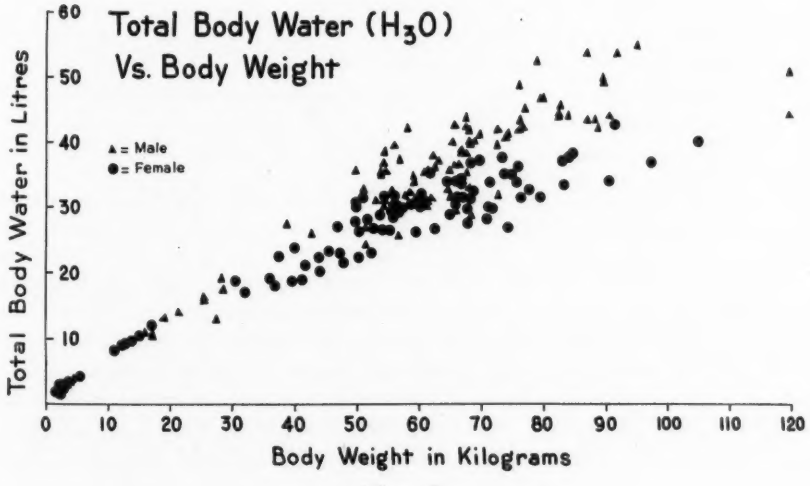

Figure 2.

Samples: Samples of heparinized blood were drawn at 1½, 2½, 3½, and 4½ hours after injection of the dose. Early in the study more frequent samples were drawn to study the characteristics of the various limbs of the equilibration curve. The samples were centrifuged in plastic containers for 20 minutes and the serum separated from the cells. One cc of plasma was pipetted into a plastic tube and the protein precipitated out with 2 cc of 10 per cent trichloroacetic acid.[2,3] This was then centrifuged again and a clear supernatant obtained. One cc of this was pipetted into 20 cc of the scintillation fluid previously placed in special 24 cc counting bottles. This was then counted in the liquid scintillation counter. The counting time was five minutes. Liquid scintillation counting is very stable and the probability of error is always below 5 per cent. Background was always below 40 cpm in a 20,000 raw count.

Standard: The standard was a limiting factor to the method. The radiation from H^3 is weak and trichloroacetic acid which we used to precipitate protein is a strong quencher, hence the standard must be made in exactly the same fashion as the samples. Since this work was completed, methods of avoiding this have appeared.[2,3]

The main advantage of their methods[2,3] is the obviation of the use of an internal standard. Since we used this standard and also proportional counting and equilibration curves in all our determinations, the lower efficiency does not affect our data; besides in the small quantity of plasma used (1 ml) the method of Langhan is superior to that of Werbin's.[3] But it is true that by the high effciency in recovery (up to 100 per cent in Werbin's) we can appreciably decrease the dosage. However, in Tritium with its low energy overdosage, it is not a problem. We prepared our own standard in a way different from Langhan.[1] Using the method of Schwartz and Moody[4] we secured pooled serum, preferably fresh, from healthy patients. To 9 cc of this we added 1 cc of a 1:500 dilution of our stock solution. This was then treated as the samples with trichloroacetic acid and 1 cc of supernate pipetted into 20 cc of liquid scintillation fluid. Depending upon the specific activities of the delivery the absolute counts were in the region of 20,000 cpm, giving a serum concentration of 0.04 μc/cc.

Calculations: The net counts were converted into serum concentration and plotted on semilogarithmic paper to obtain the equilibration curve. Extrapolation was carried to zero time and this value was used for calculating Total Body Water. Standard statistical methods were used for analysis of data.

RESULTS

Generally there were two types of curves obtained: Type I (illustrated by triangles in Fig. 1) rose quickly in a geometrical fashion to a sharp peak, fell sharply, and then flattened out. In several of the curves which were studied in detail, there were sudden small variations ("seesaws") in the limb suggesting shifts in body compartments before equilibration. Type 2 (illustrated with circles in Fig. 1) at first rose slowly and then flattened out, there were many modifications in these curves but these were all in the early limbs of the curve. These

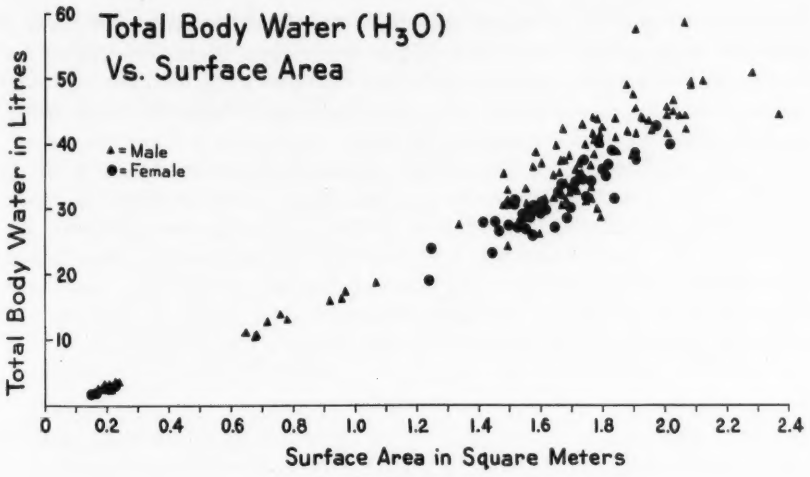

Figure 3.

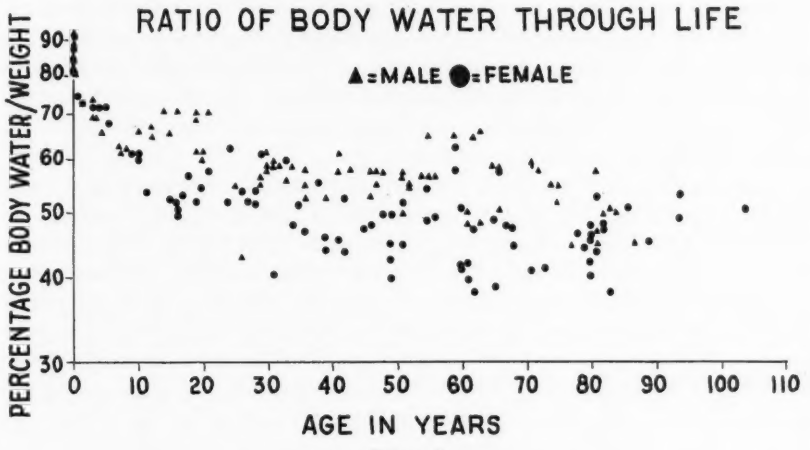

Figure 4.

curves agree very well with those of previous studies.[5,6,7] It was quite striking to note the rather stable figures in the graphs after equilibration. The average equilibration time was 90 minutes, which agrees with that for deuterium[7] and was consistently better than with antipyrine.[8]

Fig. 2 ($H_2{}^3O$ vs. Weight) illustrated the relationship between the body weight in kilograms and total body water in liters in the 200 subjects studied. As the weight increased over 30 Kg there was a dispersion of the correlation.

Fig. 3 ($H_2{}^3O$ vs. Surface Area) illustrates the relationship between the body surface area in square meters with the value for total body water in 200 subjects studied. The correlations here were far less dispersed than in Fig. 2.

Fig. 4 (Ratio of Total Body Water through life) relates the percentages of

body water in relation to weight throughout life. Highest percentages were obtained in the prematures and were 92 per cent. These figures fall uniformly in both males and females until puberty when males make a sharp ascent and the females a descent. These differentials are maintained through life with the gap gradually closing with the advancing decades.

The mean values of all 200 patients studied, arranged according to sex and age by decades together with their regression equations are presented in Table 1. As is indicated in the table, a significant difference in the percentage of body water between male and female is first seen between the ages of 11 and 20 years. This difference is maintained throughout all decades. In addition, one can see a progressive decline in the percentage of total body water with each advancing decade of life; this was more pronounced in the male than the female.

DISCUSSION

Total body water has been measured in three ways: 1) Desiccation of cadavers.[9] 2) Indirect physical and chemical methods.[13,14] 3) Dilution techniques.

The earliest determination of total body water was done by desiccation procedures and the first data was that of Bischoff[9] in 1863. He estimated the total body water at 58.5 per cent of body weight. Mitchell[10] in 1945 reported a figure of 67.8 per cent from desiccation of a 35 year old man who died in congestive heart failure. This figure has been described as high.[11] However, Widdowson in 1951[12] made similar analyses with comparable results. Needless to say, this method is limited and cannot be used *in vivo*.

In 1941, Behnke[13,14] showed that the main variable in body density was its fat content. He noted that fat had a low specific gravity (0.92) and that the determination of the body specific gravity as performed by weighing under water enabled one to calculate the fat content. Behnke's classical studies formulated the now commonly used concept of lean body mass. Rathbun and Pace[15] carried this study further. By determining the specific gravity and the actual fat contents of guinea pig carcasses over a wide range of body weights and degrees of obesity, they derived an empiric formula for determining body fat from the specific gravity:

$$\% \text{ Fat} = \left(\frac{5.548}{\text{sp. gr.}} - 5.044 \times 100 \right) \tag{1}$$

Since it was demonstrated previously by several workers[16,17,18] that lean body mass had an almost constant fraction of water (73.2 per cent), it is possible to express the percentage of fat by means of the following equation:

$$\% \text{ Fat} = 100 - \frac{\%\text{TBW}}{0.732} \tag{2}$$

By substituting expression (2) for the original empiric formula above in equation (1), the Pace formula was derived and has been used for calculating total body water from a single measurement of body specific gravity:

$$\% \text{ Water} = 100 \left(4.424 - \frac{4.061}{\text{sp. gr.}} \right) \tag{3}$$

This method is very limited in its application because it requires elaborate equipment and a patient sufficiently robust and in good health to endure total submersion and to maintain complete expiration long enough to permit measurement of the amount of displaced water.

The best method of measuring total body water *in vivo* is by the dilution technique.[5,6,7] An exact quantity of a substance which will diffuse evenly into the compartments of body fluid is injected. At equilibrium, a sample of blood is withdrawn and the calculation of the volume of distribution is made by the simple chemical formula where

$$C_1V_1 = C_2V_2$$

C_1 = initial concentration $\quad$ C_2 = final concentration
V_1 = initial concentration $\quad$ V_2 = final concentration

Several substances have been used for this purpose. Antipyrine[19] and its derivatives N-Acetyl-4-amino-antipyrine (NAAP) have been used for estimating total body water. Antipyrine is cheap and the chemical determination is comparatively easy but it has the disadvantage of being rapidly destroyed in the body. Therefore, extrapolation of its disappearance curve back to zero time becomes an arbitrary correction. Other substances used in the past have included urea,[20] thiourea,[21] and sulfanilamide.[22,23] Urea is difficult to use because the body forms its own urea rapidly. Thiourea is destroyed within the body and sulfanilamide is known to enter cells in unequal ratio to the extracellular concentration.

More recently, the use of isotopes of hydrogen for labelling water in the determination of total body water has become the principal tool. Hydrogen has two isotopes, H^2 and H^3. H^2 or deuterium, is used in form of deuterium oxide or heavy water. Hevesy,[24] Moore,[7,25] Hardy,[26] and Solomon[27] have all used deuterium with excellent results.

We have presented the results of the clinical application of our modification of Langhan's[1] method of determining total body water with Tritium Oxide ($H_2{}^3O$, HTO). This method is simple, accurate and very reproducible. The fear of the long physical half life of tritium oxide is not well founded since this is really an advantage. The long physical half life enables deliveries of this isotope to be easily made, and storage for as long as several years will not disturb the isotope (decay after one year of storage is less than 4 per cent). The biological half life, however, is only 2 to 19 days (mean—9 days), depending upon the intake of water.[4] The energy output of tritium is very low, 0.0179 m.e.v. (1/40 as much as I^{-131}) and this energy, is all soft beta rays which can be shielded with the thickness of a single layer of tissue paper. The dosage rate for a 70 Kg. man is 0.009 reps per day. Total dose is 0.25 reps; the heaviest concentrations are in the gastric juice and the stomach wall is particularly resistant to radiation.

Using this simple method we have related total body water to age. Several workers have had individual series showing the relationship of total body water to the various body compartments and sex; we have carried this further to relate it to age, thus expanding its scope in the better understanding of metabolism and aging. Several points are significant in this study.

TABLE I. MEAN VALUES OF GROUPS OF TEN PATIENTS IN EACH DECADE STUDIED

Group	MALE									FEMALE								
						REGRESSION EQUATION									REGRESSION EQUATION			
	Age	Weight (Kg)	Surface Area (Sq. meters)	Total Body Water (in liters)	% Body Water	TBW	r	t	p	Age	Weight (Kg)	Surface Area (Sq. meters)	Total Body Water (in liters)	% Body Water	TBW	r	t	p
Premature & Newborns	41 hrs.	3.17	0.20	2.75	86.8	0.634 (wt) + 0.65	0.734	4.585	< 0.001	46.6 hrs.	2.77	0.19	2.31	83.9	0.423 (wt) + 6.22	0.875	24.11	< 0.001
1-10 Yrs.	5.6	21.53	0.82	13.	64.86	0.57 (wt) + 1.65	0.967	10.735	< 0.001	6.1	20.97	0.804	13.66	69.66	0.56 (wt) + 1.92	0.999	63.198	< 0.001
11-20 Yrs.	16.4	57.94	1.64	37.96	65.83	0.51 (wt) + 8.41	0.961	9.829	< 0.01	16.4	54.84	1.56	28.70	52.46	0.47 (wt) + 2.93	0.982	14.705	< 0.001
21-30 Yrs.	27.2	77.52	1.91	43.65	57.54	0.24 (wt) + 25.05	0.751	3.217	< 0.025	26.9	57.69	1.606	31.60	54.88	0.42 (wt) + 7.37	0.912	6.289	< 0.001
31-40 Yrs.	34.4	76.9	1.91	44.6	57.20	0.50 (wt) + 5.71	0.833	4.258	< 0.005	34.9	65.33	1.643	30.92	48.51	0.29 (wt) + 11.97	0.867	4.921	< 0.005
41-50 Yrs.	45.4	69.64	1.814	39.24	56.39	0.41 (wt) + 10.69	0.940	7.793	< 0.001	45.9	72.40	1.747	33.01	46.05	0.30 (wt) + 11.29	0.894	5.643	< 0.001
51-60 Yrs.	53.5	70.81	1.825	40.47	57.39	0.39 (wt) + 12.85	0.803	3.811	< 0.010	56.6	63.73	1.601	31.91	50.56	0.13 (wt) + 23.63	0.315	0.939	< 0.40
61-70 Yrs.	64.2	70.72	1.79	37.89	54.49	0.27 (wt) + 18.80	0.892	5.581	< 0.001	64.6	67.77	1.673	29.59	44.65	0.261 (wt) + 11.97	0.790	3.644	< 0.010
71-80 Yrs.	73.1	69.86	1.776	35.26	52.2	0.24 (wt) + 18.49	0.823	4.098	< 0.005	77.7	63.09	1.633	27.87	44.0	0.39 (wt) + 3.26	0.966	10.568	< 0.001
81+ Yrs.	83.6	59.61	1.66	29.51	49.84	0.15 (wt) + 20.57	0.303	0.899	< 0.40	87.6	51.76	1.46	24.36	45.88	0.30 (wt) + 8.83	0.927	6.995	< 0.001

Legend:

TBW = Total Body Water
r = Correlation Coefficient (1.0 = maximal significance)
t = Significance of Regression Equation
p = Probability (0.001 = maximal significance)

First, we have noted an absolute and relative decrease in total body water with age. At first we were quite reluctant to accept this conclusion which is very well illustrated in Table I. The data, however, is incontrovertible. The male and female prematures and newborns show no significant difference in the water content. They have one thing in common; i.e., a very high total body water content. At the end of the first year, there is a sharp drop in this condition and the water content gradually rises again until puberty (Fig. 4). Previously, most writers accounted for the sharp separation of the sexes as due to the development of the fat in the female with the onset of puberty and the development of secondary sex characteristics. We find that besides this factor another major factor is the greater development of muscles mass in the male. This is particularly well illustrated in one patient we studied; a 35 year old negro male who was a boxing instructor and still in excellent physical condition. He weighed 79.1 Kg., and had a very high value of 52.4L of total body water with an excellent equilibration curve. The percentage was 66.3 as opposed to a mean of 57.2 for his age decade. He had over nine per cent more water than the average, and the group was not particularly obese (mean weight 76.9 Kg.). In Fig. 4, the percentage of body water for the male after 11 years of age actually rises above the mean as much as this percentage for the females falls below this mean.

The argument is further revealing when the general data is studied. For some reason people have considered women more obese than men, probably from such old wives tales as the bilious concept of "fair–fat–forty." Throughout the data the mean weights of the males are usually higher than the corresponding weights of the females in the various decades. This may be due to the fact that the women (at least in the American milieu) are more conscious of their weights than the men. The total body water differed not only because of the obesity of the female but also due to the larger muscle mass of the male.

One very practical point was made evident here. Total body water is directly proportional to total body potassium[28] which in turn is proportional to lean body mass which in turn is proportional to total blood volume (here Red Cell Mass and Plasma Volume). Total body water decreased with age, and, therefore, blood volume decreases with age. In transfusing these elderly patients, age is an important factor. Too often an ideal blood volume of a 21 year old medical student is used as an ideal for an elderly man. One example made this clear to us. A 72 year old male patient had a carcinoma of the esophagus proved by biopsy. He was diagnosed early and had not lost much weight. The tumor was resected under hypothermia and his stomach anastomosed to the esophagus in the neck after bringing it up through the right chest. He withstood the operation very well and lost some blood which we attempted to replace. A blood volume was done a few hours after surgery and a deficit (based upon the ideal blood volume of a young man) was reported at 1500 cc. The patient, however, appeared much better clinically, running a pulse of just slightly under 100. We elected to recheck the calculation based on the regression equation; the deficit figure was even higher. We elected to neglect these figures and not transfuse the patient and he made an excellent recovery. Several other cases like this have shown the dangers of neglecting the effect of age on the water balance of our patients.

SUMMARY

We have used Tritium Oxide ($H_2{}^3O$) as sterile distilled water to study total body water by the liquid scintillation method of Langhan as adapted by us. The subjects were 200 patients ranging in age from a three month premature to a lady, 104 years old. These subjects were free from electrolyte or water imbalance.

The new isotope is cheap, easily measured and gives a very reproducible result. It can be used clinically and is not dangerous either to give or handle.

Our data shows a progressive decrease in the percentage of total body water with advancing decades of life. It commences as high as a mean value of 86.8 per cent in premature and newborn males and as low as 49.8 per cent in males past 81 years of age. The corresponding values in the female were 83.9 and 45.8 per cent.

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Announcement to Authors

Preliminary Notes

Space will be reserved in each issue of THE JOURNAL OF NUCLEAR MEDICINE for the publication of one preliminary note concerning new original work that is an important contribution in Nuclear Medicine.

Selection of the preliminary note shall be on a competitive basis for each issue. One will be selected after careful screening and review by the Editors. Those not selected will be returned immediately to the authors without criticism. Authors may resubmit a rejected or revised preliminary note for consideration for publication in a later issue. The subject material of all rejected manuscripts will be considered confidential.

The text of the manuscript should not exceed 1200 words. Either two illustrations, two tables, or one illustration and one table will be permitted. An additional 400 words of text may be substituted if no tables or illustrations are required. Only the minimum number of references should be cited.

Manuscripts should be mailed to the Editor, Dr. George E. Thoma, St. Louis University Hospital, 1325 South Grand Blvd., St. Louis 4, Missouri. They must be received before the first day of the month preceding the publication month of the next issue, e.g., preliminary notes to be considered for the March, 1963 issue must be in the hands of the Editor before February 1, 1963.

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Variability in Renal Clearance Rate Studies Using Fresh OI^{131}HA, Purified Product, and Stored Product[1,2,3,4]

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INTRODUCTION

For several months we had been performing renal clearance studies with radioiodinated hippuran (OI^{131}HA) and making comparison studies with renal clearance of para-amino-hippuric acid (PAH) and inulin. The method used for obtaining hippuran clearances was that outlined by Smith (1). After comparable and reproducible results were obtained, there ensued a period during which no consistency was obtainable employing identical techniques. At the same time, the radioisotopic renograms which we were performing on patients likewise became inconsistent in their appearances. It occurred to us that this might be related to impurities contained within the radioiodinated hippuran, especially free iodide. A method was therefore developed for quantitation of the free iodide contamination of the radioiodinated hippuran, and these results were thereafter checked by the paper chromatography technique of Burbank, Tauxe, Maher, and Hunt (2). In this pilot study it became apparent that there was considerable contamination with free iodide (approaching 25 to 30 per cent on occasion), and it was decided that a systematic study of the extent of contamination, and the effect of such contamination on renal clearances as well as on radioisotopic renograms would be undertaken.

The radioactive hippuran was secured from two commercial sources, and little difference was noted between them, although most of the experiments were conducted with the sodium orthoiodo^{131}-hippurate obtained from one source.

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[1]From the Departments of Radiology and Physiology Bowman Gray School of Medicine, Wake Forest College, Winston-Salem, North Carolina.

[2]Under grant-in-aid from U.S.P.H.S.N.I.H.–5418 And N.C. Fluid Research.

[3]Presented at the 9th Annual Meeting, Society of Nuclear Medicine, Dallas, Texas, June 29, 1962.

[4]With assistance by Mrs. Norma Greenwood, Mr. Claudius D. Walker, and Mrs. Donna Schmid.

Because any free I^{131} present would be counted as though it were on the hippuran molecule it is obvious that deviation in clearance values could result, since free iodide instead of being excreted by the renal tubules, as is the case with hippuran, would be partially reabsorbed from the glomerular filtrate, thereby rendering the radioactivity of the urine relatively low and that of the plasma relatively high. Thus a high content of free iodide in the test agent might be expected to give low hippuran clearances and to modify the radioisotopic renogram accordingly. Burbank, et al. (2) found that the differences between the PAH and $OI^{131}HA$ clearances generally increased as free iodine content increased from 8.4 per cent with less than 2 per cent free iodide, to 20.3 per cent with more than 5 per cent free iodide. It was obvious to them that the deviation of radiohippuran clearance values from expected values was much more pronounced in those clearances performed with lots of the commercial hippuran reagent that contained large amounts of free iodide. Iodide renal clearance in normal persons has been shown to average only 31 ml per minute (3). As a result of these low clearances, plasma iodide increases relatively rapidly at high levels of administration.

Moreover if there is free iodide in the test reagent, the radiation to the thyroid would increase particularly if the thyroid has not been previously saturated with Lugol's solution.

METHOD

A simple technique was developed for the determination of free radioiodine in radioactive ortho-$iodo^{131}$-hippurate, and the results were checked qualitatively against the paper chromatography method of Burbank, et. al. (2).

The paper chromatography technique is as follows: The reagent is applied on 2 cm strips of Whatman #1 paper and developed vertically for at least four hours in N-Butanol saturated with IN-acetic acid. In this system, hippuran has an average Rf value of 0.84, iodide of 0.20. After they were dried, the strips were cut up into 5 mm strips, weighed, and assayed with a scintillation well counter. The radioactivity in each small strip was normalized and then quantitated. These activities were graphed, and the areas under each Rf portion determined by planimetry.

The method for determination of free radio-iodine chemically was as follows: A solution of any countable fraction of the radioactive OIHA in 2 ml of water is swirled with a saturated solution of non-radioactive elemental iodine in 2 ml of carbon tetrachloride (CC14) for approximately 3 hours at 25 degrees C. which allows equilibration to occur. Experimental results indicate that essentially all of the radioactivity originally in the form of contaminating radio-iodide will have exchanged into the CC14 solution of iodine under the conditions of the experiment. A one ml aliquot of the CC14 layer is carefully removed at the end of equilibration and 0.5 ml of this is counted for determination of radio-iodine contamination.

$$\%\ I^{131}\ \text{contamination} = \frac{4X\ (\text{counts in CC14-Iodine aliquot})}{(\text{counts in original solution of radioactive OIHA})}$$

(An appropriate factor other than the "4" in the formula may be substituted if more or less than the 0.5 ml is used with respect to the total quantity of 2 ml.)

For removal of free iodide, a technique has been devised as follows: Just prior to use, the radioactive OIHA solution is diluted to 5 ml and treated with a freshly-made suspension of silver chloride (approximately 3 grams) and filtered. The silver chloride is washed twice with 2 ml each of sterile distilled water. In this way, contaminating sodium radio-iodide is converted to sodium chloride by ion exchange. Tests indicate the free radio-iodide to be reduced to 1 per cent or less.

After initial exploratory experiments convinced us that free radio-iodide could be appreciable in commercially available radioactive OIHA, and after qualitative chromatographic studies confirmed these results, an experiment was designed to determine the following:

(1) The free radio-iodide content of several commercial shipments of radioactive OIHA with varying specific activities—high, low, and intermediate—was determined upon receipt and frequently thereafter over a period of approximately ten weeks. These samples were stored in a dark safe in an air conditioned room.

(2) The radio-iodide content of the "purified" compound was always determined thereafter—and just before experimental use in animals.

(3) After renal clearance rates for "purified" radioactive OIHA were well established on a group of trained unanesthetized dogs, the OIHA was contaminated with known quantities of free iodide and clearances once again determined after Lugolization of the dogs. The percentage variation from the normal for these animals was thereafter calculated.[1]

(4) Simultaneously with the renal clearance studies, radioisotopic renograms were also performed on these unanesthetized dogs and the radioisotopic renograms so obtained were compared with the earlier unmodified radioisotopic renograms in these same animals.

DESCRIPTION OF RESULTS

The three specific activities of the radioactive hippuran studies were: 0.12 mc/mg; 0.46 mc/mg; and 1.27 mc/mg. Figure 1 illustrates a steadily increasing percentage of free iodide in each batch as follows: The intermediate (0.46 mc/mg) and highest (1.27 mc/mg) specific activity samples increased until the 42nd day and seemed to plateau beyond that point at approximately 8 per cent free iodide.

The lowest (0.12 mc/mg) specific activity plateaued at approximately the 25th day with 6 per cent free iodide.

The intermediate specific activity curve was very slightly higher than the highest specific activity, but the differences were small and the slopes practically identical.

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[1]A modified technique for $OI^{131}HA$, clearance rate has been developed employing a single injection technique, but this will be described in a separate communication.

The lowest specific activity material always had a significantly lower free iodide content and its slope was appreciably different.

The lowest specific activity material consistently was reduced to less than 1 per cent free iodide throughout the study period by the filtration and purification procedure.

Coincidentally iodine 125-labeled OIHA was also studied for free iodide and at no time was the free iodide in this solution found to be greater than 1 per cent.

Table I indicates the effect of various percentages of known free iodide upon the determined average clearance rates on four of the unanesthetized animals studied. It will be noted that the percentage suppression of recorded clearance (whole blood) ranged between 44 per cent for 10 per cent free iodide to 94 per cent for 60 per cent free iodide.

When one plots the reciprocal of the percentage suppression (which actually represents the contaminated clearance result divided by the original uncontaminated clearance result times 100) one finds virtually a straight line exponential function (Fig. 2). This would suggest that there is an exponential relationship between percentage of free iodide and the recorded hippuran clearance.

A somewhat similar but less defined straight line exponential function is observed when one plots the actual clearance values obtained with the contaminated hippuran as against the uncontaminated which further verifies the concept that there is such a straight-line exponential relationship (Fig. 2). The superimposed radioisotopic renograms are also quite interesting.

With the 5 and 10 per cent contamination it is very difficult to actually detect

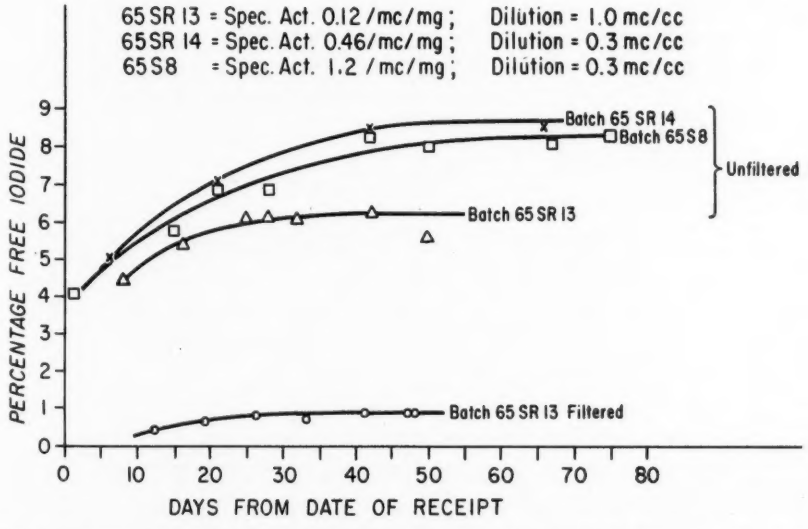

Fig. 1. Percentage free iodide in three different batches of OI^{131}HA of varying specific activities over a period of approximately 10 weeks (stored in light-tight safe, air conditioned atmosphere).

TABLE I

CHANGES IN HIPPURAN CLEARANCE RATES IN UNANESTHETIZED TRAINED DOGS BEFORE AND AFTER ADDITION OF VARYING PERCENTAGES OF FREE IODIDE

Dog No.	*Ave. Clearance* (whole blood) With 1% or Less Free Iodide c.c./min.*	*No. of Different Determinations*	*Ave. Clearance* (whole blood) with Iodide, Comb.*			*Clearance Rate with Contaminated Hippuran × 100 Clearance Rate with Purified Hippuran*	*% Suppression*
			% Free Iodide	*Clearance c.c./min.*	*No. of Determinations*	%	
1	156	3	10	87	1	56	44
2	203	7	39	39	1	19	81
			56	22	1	11	89
3	228	3	15	138	1	60	40
9	241	7	48	31	1	13	87
			60	14	1	6	94

*Actual Values—No correction for Surface Area

any significant difference between the radioisotope renogram so obtained and that obtained with the purified product. However, when one utilizes 15 per cent free iodide contaminated OI^{131}HA, one finds that the peak time is somewhat prolonged and there is a somewhat greater slope on the down phase (excretory phase) of the radioisotopic renogram curve. As one increases the percentage of free iodide beyond this level one finds that the peak is depressed in the so-called "secretory phase" to the point where it is no longer recognizable with the higher contamination levels. Moreover the excretory phase is considerably prolonged and its obliquity moves toward the horizontal so that ultimately with the higher percentages of free iodides, a normal radioactive radioisotopic renogram is no longer obtained. (Fig. 3)

The effect of auotclaving the purified filtrate was also studied and in this experiment it was found that autoclaving the filtrate for 15 minutes at 20 pounds steam pressure results in an increase of free iodide from less than 1 per cent to an average of 4½ to 5 per cent thus negating the benefits of filtration to a great extent, depending upon the initial free iodide present.

DISCUSSION

From this study it would appear that the most desirable radioactive labeled hippuran is: 1) The low specific activity ortho-iodo^{131}-hippurate; 2) or possibly that OIHA which is labeled with I^{125}.

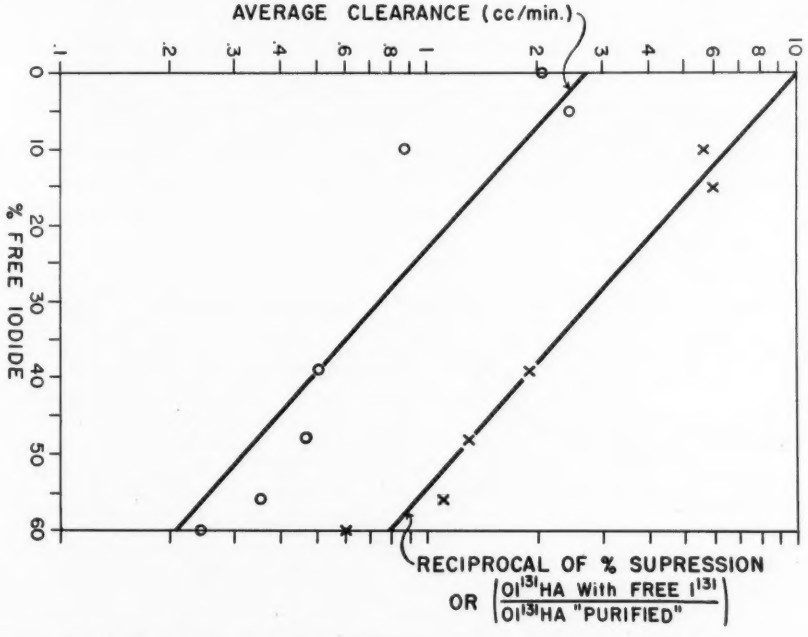

Fig. 2. Relationship between OI^{131}HA clearance rates and percentage free iodide.

Since external monitoring over the kidney becomes somewhat more difficult with I^{125}, our own experiments have been very limited with this label, but Winter and Myers (6) are apparently able to obtain radioisotopic renograms with this label, employing special scintillation probes, although the complete satisfaction with this label remains to be proved.

Even with the low specific activity material a maximum of approximately 6 per cent contamination is reached when the shelflife exceeds 25 days storage at 68 to 70 degrees F., in a dark safe, in an air conditioned atmosphere. Filtration is satisfactory for purification in accordance with the technique described, provided one does not have to autoclave the resultant filtrate.

There is a suppression of recorded $OI^{131}HA$ clearance by free iodide^{131} in accordance with an exponential function giving a straight line, on a semi-logarithmic plot.

There is also a suppression of the normal radioisotopic renogram so that the secretory peak time is prolonged and diminished in height, and the excretory phase of the renogram is markedly prolonged approaching the horizontal.

Magnusson (4) also showed that the radio-renogram curves showed a tendency to flatten out after the injection of solutions contaminated with free radioiodide. The initial rise in the uptake phase did not reach the same level as when a pure solution was administered. Also the excretory component decreased slower so that this resulted in a higher radioactivity level from 7 to 11 minutes than was the case when using the pure radio-hippuran. The urine radioactivity estimations also established that higher content of free radioactive-iodide in the radiohippuran resulted in lower values of excreted radioactivity.

It is our present contention that it is obligatory to assay the ortho-iodo^{131}-

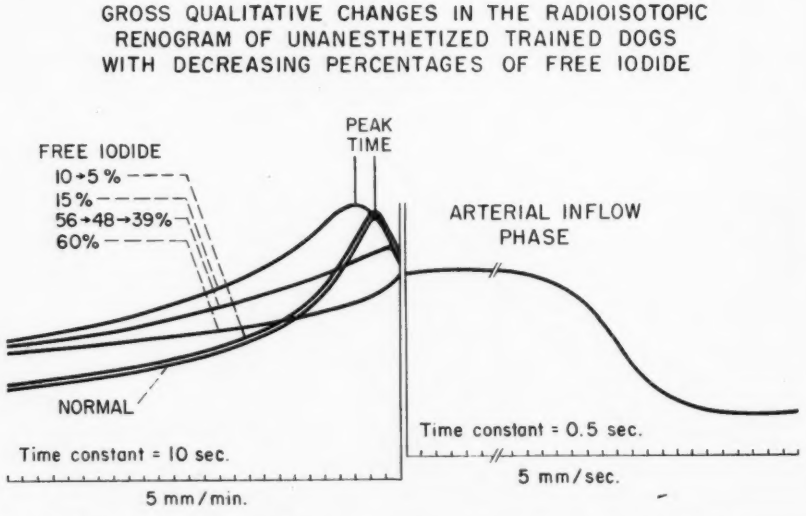

Fig. 3. The qualitative effects of varying percentages free iodide on the $OI^{131}HA$ renogram (superimposed normalized tracings)

hippuric acid labeled compounds for free iodide^{131} and record same until it is known what effect this may have on such further studies as may be done with this compound. It is certainly our further recommendation that low specific activity ortho-iodo^{131}-hippuric acid be employed wherever possible.

SUMMARY

Three different specific activity materials were studied of I^{131}-labeled sodium ortho-iodo^{131}-hippurate. These showed a gradual increase of free iodide^{131} in the course of time under standard conditions of shelf storage in an air conditioned atmosphere. A maximum of 8 per cent free iodide then was recorded with the higher specific activity materials employed in this study, although on previous occasions free iodide as high as 25 and 30 per cent was noted in some of the older materials used.

The best results are obtained with the low specific activity materials, but even here in the course of 25 days, a 6 per cent free iodide^{131} was noted.

A method is described for diminishing the free iodide^{131} to less than 1 per cent; and similarly a method is described for assaying the percentage of free iodide^{131} present in the compound utilized.

As the result of the purification process less than 25 per cent of the hippurate is lost with the filter.

There is a very marked suppression of clearance rates determined with I^{131}-labeled OIHA by the free iodide^{131} so that one must be certain that the free iodide^{131} present is less than 1 per cent for reproducible and easily interpretable results. On the other hand, it is probable that an appropriate correction can be made if the percentage of free iodide^{131} is known, by employing the straight-line exponential correction relationship demonstrated.

It is virtually impossible to obtain a satisfactory radioisotopic renogram when the percentage of free iodide^{131} is in excess of 15 per cent. Under these circumstances quantitation of the various phases of radioisotopic renogram are impossible on a reproducible basis.

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JOURNAL OF NUCLEAR MEDICINE 4:78-81, 1963

The I^{125} Radiopulmonogram[1,2]

**Maurice J. Small, M.D., Wade N. Miller, M.D., George C. Leiner, M.D.
Herbert D. Strauss, A.B. and Sol Abramowitz, B.S.**

East Orange, New Jersey

A new technique, Radiopulmonography, has been described by this laboratory for the simultaneous estimation of the ventilation of individual portions of both lungs (1,2). Radiopulmonography utilizes a portable x-ray machine operating at approximately 25 KV and less than 0.5 ma, as a source of "soft" radiation. The x-ray source is placed 6 feet in front of the chest wall, and the exit beam is measured by a dual scintillation detection system with probes placed over corresponding areas of both lungs. Respiration alters the linear density of the lung tissue and thereby alters the intensity of the exit beam. Inspiration decreases the linear density and increases the exit dose while expiration increases the linear density and decreases the exit dose. Characteristic curves have been obtained for the normal and for various disease states.

A major technical problem in the development of this procedure has been variation in output of the x-ray machine. To a major extent this problem has been solved by the installation of a good AC line voltage regulator in the supply line to the x-ray machine. Changes in x-ray output shift the baseline of the curve, and make frequent slight adjustments in milliamperage necessary. Attempts to quantitate these studies, in an effort to carry out ventilation and volume determinations by this technique, have been rendered difficult by the variation in baseline of the curve depending on x-ray output. Because of this problem, we have considered replacement of the x-ray machine with an external radioisotope source which would have a constant output. The isotope to be used for such a study should have the following characteristics: 1. It must have soft gamma radiation to reproduce the phenomena obtained with the x-ray machine. 2. It must have a sufficiently long half-life to make it economically feasible. 3. It must be readily available. 4. It should preferably have no appreciable beta component.

I^{125}, in which there has been considerable interest recently (3), seems to meet these requirements. I^{125} decays by electron capture to produce a 27.4 KEV x-ray and a 35.4 KEV gamma ray with no beta emission. These photons are in the desirable range for this study. The half-life of I^{125} is 60 days which is probably long enough so that source replacement would not be a major problem, and the isotope is becoming increasingly available as new compounds are being synthesized with it.

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[1]From the Radioisotope and Cardiopulmonary Laboratories, Veterans Administration Hospital, East Orange, N. J.

[2]Preliminary Progress Note. (See page x).

A source of I^{125} consisting of 46 MC was used for this study.[1] The isotope was in a volume of about 1.5 ml and was placed 14 inches in front of the chest wall. Dual scintillation detectors were placed as previously described, and characteristic breathing curves were obtained. Because the source is so near to the chest and not 6 feet away as in the x-ray tube, it was found necessary to keep the

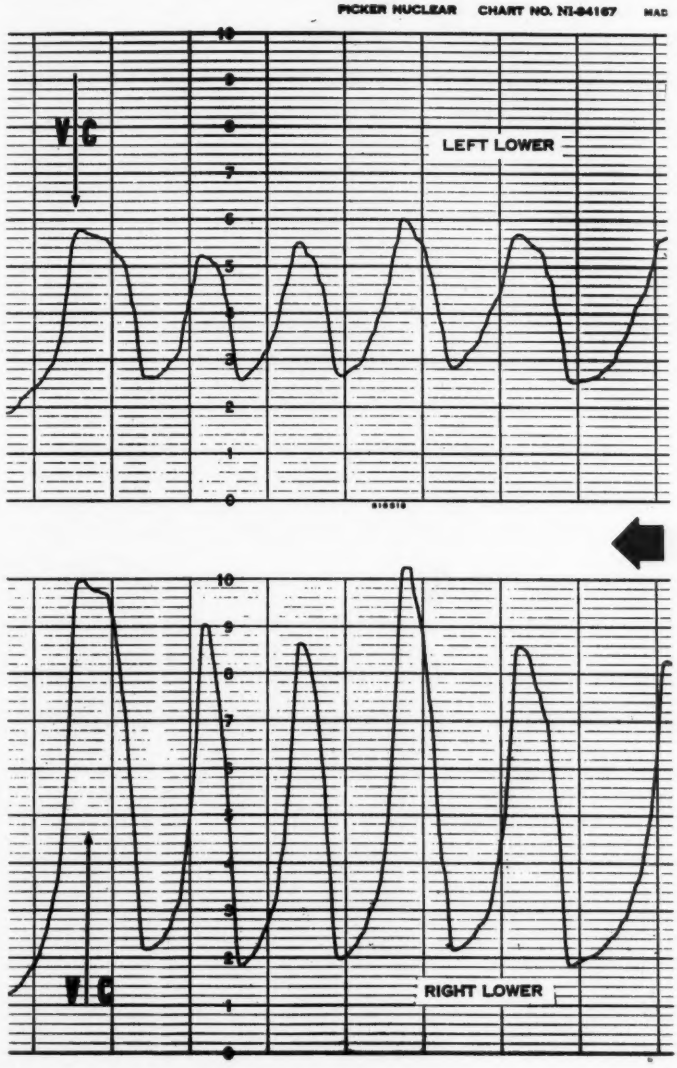

Fig. 1. Essentially normal tracing. V.C. = vital capacity.

[1]Generously loaned by Dr. Paul Numerof, E. R. Squibb & Sons.

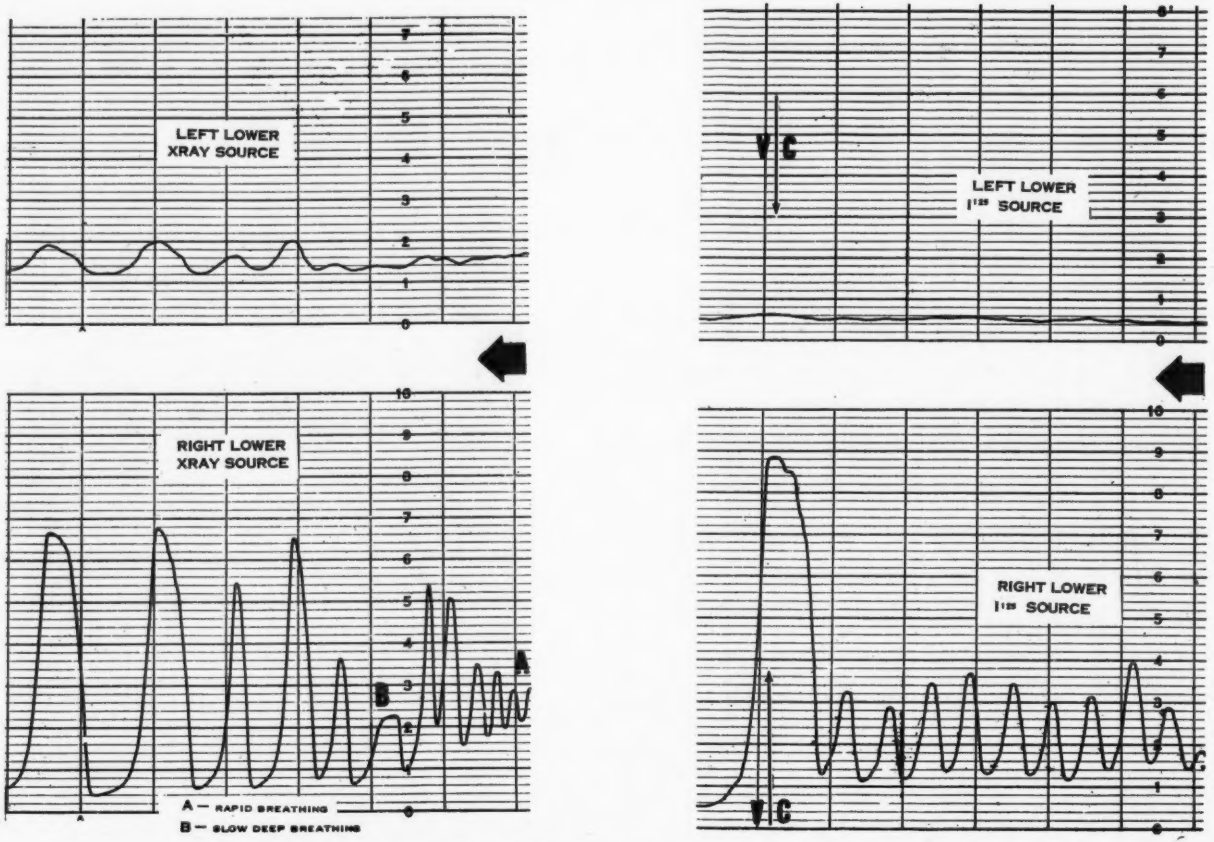

Fig. 2. Tracing showing marked impairment of ventilation of the left lung, demonstrating comparable findings with an x-ray source and with I^{125} source. V.C. = vital capacity.

source on an exact horizontal plane with the detectors. This necessitates moving the source when changing probe positions so that it remains exactly opposite the probes. With the present cost of I^{125} it would be prohibitive to use a source large enough so that the 6 ft. distance could be maintained.

Figure I demonstrates an essentially normal tracing. The diminished amplitude over the left lower lung field as compared to the right has been seen in normal subjects and is attributed to the decreased lung volume over the left lower chest resulting from the presence of the heart.

Figure 2 shows that qualitatively similar tracings are obtained regardless of whether one uses I^{125} or x-ray as the source. This tracing was obtained from a patient with extensive and disseminated healing tuberculous lesions throughout the left lung, with a contracted and shrunken left hemithorax. Both tracings well illustrate the marked reduction in ventilatory excursion over the diseased left lung and pleura. The differences in amplitude of the curves is not of significance since this varies with the distance of the I^{125} source from the patient or with the milliamperage used with the x-ray source. The significant information is the difference between the two lungs and this is well brought out by either source.

Whether an I^{125} source will prove to be preferable for studies of this kind remains to be determined by further study. Its major advantages, of course, are light weight and portability of the source, constant energy output and convenience. On the other hand it is extremely directional and the only control the operator has to adjust the amplitude of the curves as one goes from the small deflections at the apex to the larger deflections at the base is to move the source closer or further from the patient or change the scaling factor of the recording device. The latter however varies by a factor of three, so that slight adjustments are difficult to make.

On the other hand, the advantage of an x-ray source is that the distance from source to patient can be kept constant and small adjustments to vary the amplitude of the curves depending upon the area of lung studied or the nature of the disease process can be made by controlling the milliamperage, and the source can be more easily controlled. Only further studies with both methods will indicate which will prove to be better for clinical use. At the present time it is considered of interest to report that with only 1 or 2 ml of radioactive solution and a commonly used dual scintillation detection system it is possible to obtain in a matter of minutes curves that appear to reflect the ventilation of portions of each lung.

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ETUDE CRITIQUE DES TESTS DE L'ABSORPTION INTESTINALE UTILISANT LA TRIOLEINE I-131 ET L'ACIDE OLEIQUE I-131. (A CRITICAL STUDY OF TESTS OF INTESTINAL ABSORPTION UTILIZING I-131 TRIOLEIN AND I-131 OLEIC ACID.)

GRENIER J. F., HATANO, M. & WEISS, A. G.: *La Presse Medicale* **70**:42, 1962.

The authors studied the absorption of inorganic iodine from I-131 labelled triolein and oleic acid introduced in doses of 100 microcuries into the lumen of isolated loops of small and large intestine of dogs.

By simultaneous sampling of the portal vein, the mesenteric vein of the isolated loop, the inferior vena cava, the thoracic duct and the mesenteric artery, the authors demonstrated a significant and early absorption of inorganic I-131. The highest concentrations were found in the mesenteric vein, and these were consistently above those found in the mesenteric artery.

On incubating the I-131 labelled triolein and oleic acid with bile, pancreatic and intestinal secretions and homogenates of liver, pancreas, and gut either simply or in combination, the highest liberation of free iodine was obtained with cellular homogenates in the presence of bile. These results suggested that this dehalogenation of the labelled fats occurred either at the surface or inside the cells of the intestinal mucosa.

Thus, they conclude that I-131 labelled triolein and oleic acid are unstable compounds which liberate most of their label in the intestinal lumen and are unsuitable for the study of intestinal absorption. Furthermore, the behavior of iodinated (stable) fats is different from that of noniodinated fats in the gut.

Finally they suggest the use of C-14 labelled triolein and oleic acid in the evaluation of intestinal absorption.

Abstracted by Jose Martinez, M. D., Johns Hopkins Hospital, Baltimore.

USE OF RADIOACTIVE XENON FOR STUDIES OF REGIONAL LUNG FUNCTION.

DOLLERY, C. T., HUGH-JONES, P. & MATTHEWS, C. M. E. *Brit. Med. J.*, p. 1006, Oct. 20, 1962.

In 1957 the noble gas, Xe-133, was first used by Knipping to measure the adequacy of ventilation in different regions of the lungs. Subsequently, oxygen-15, both as O_2 and CO_2, has been used for this purpose at Hammersmith Hospital, while Ball and his associates have improved the Xe-133 method. The Hammersmith group now use both Xe-133 and O-15 and have compared the usefulness of each in studying regional ventilation and blood flow in the lungs. To measure regional ventilation, Xe-133 is rebreathed in a closed system and the rate of wash-out after discontinuation is measured with two pairs of 1½ × 1 inch crystal scintillation detectors placed against the chest wall. To measure blood flow, a saline solution of Xe-133 is injected intravenously into an axillary vein or the superior vena cava. The patient holds his breath long enough for the Xe-133 to reach a plateau at various regions of the lungs. A comparison of the results obtained with xenon 133 and O-15 labelled gases in normal subjects and in patients with mitral stenosis, large lung bullae, bullous emphysema, and primary emphysema yielded consistent findings. Patients with mitral stenosis had a reversal of the normal pattern of low blood flow through the upper zones of the lungs compared to higher flow at the lung bases. In lung disease, unsuspected regional ventilation abnormalities were found by both methods.

The main practical advantage of xenon lies in its longer half-life (5.4 days) in contrast to the two minute half-life of O-15. The reviewer does not agree that "the collimation possible with xenon cannot compare with the small cylinders of lung that can by studied by using the positron annihilation radiation of O-15 with coincidence counting." The 30 and 80 kev gamma emissions of Xe-133 can be readily collimated. The authors also state that Kr-85 "emits only non-penetrating electrons," ignoring the gamma radiation that

is emitted 1/200 of the time. This gamma radiation makes it possible to employ *external* detection of Kr-85 as well as counting of blood samples. Nor is xenon "useless for detecting left to right cardiac shunts." While CO_2^{15} may be more useful, xenon has been used by Braunwald and others for this purpose; however, samples must be obtained by means of a catheter on the right side of the heart.

Despite these points of disagreement, the reviewer recommends the article as a worthwhile presentation of the use of the increasingly important radioactive noble gases.

Abstracted by Henry N. Wagner, Jr., M. D., The Johns Hopkins Hospital, Baltimore.

TRITIATED BILIRUBIN: PREPARATION & PHYSIOLOGICAL STUDIES.

GRODSKY, G. M., CARBONE, J. V., SANSKA, R. & PENG, C. T. (Radioactivity Research Center, University of California Medical Center, San Francisco)

Triated bilirubin was prepared by the direct Wilzbach technique, achieving a specific activity of 100 μc/mgm. Co-60 irradiation did not improve the efficiency of tritiation. Radiochemical purity of the bilirubin-H3 was demonstrated by paper chromatography. The evaluation of this material as a biological tracer proved difficult due to the lack of any sensitive colormetric methods for comparative determinations. On injecting high doses of radioactive and carrier bilirubin intravenously in rats, the biliary excretion was usually between 25 and 61 μgm/100 gm/min. There was a large discrepancy between the retained label in the serum and the colormetrically measurable bilirubin, perhaps due to tritium exchange between bilirubin and serum albumin molecules. After 75 minutes, 20 to 30 per cent of the initial label remained in the serum as non-bilirubin radioactivity. In vitro pre-equilibration of bilirubin-H3 with albumin removed the labile tritium; the distribution of the bilirubin-H3 and unlabeled bilirubin was measured colormetrically. The half-life of bilirubin in rat serum was 25 to 35 minutes.

Abstracted by John G. McAfee, M. D., The Johns Hopkins Hospital, Baltimore.

PREPARATION & PURIFICATION OF HIGH SPECIFIC ACTIVITY INSULIN-131 IODINE.

BANERJEE, R. M. & GIBSON, K., J. *Endocrinol.* **25**:145, 1962.

For the immuno assay of plasma insulin, high specific activity insulin-I-131 is essential. Previously developed micro-diffusion techniques are theoretically limited to a maximum iodination efficiency of 50 per cent. A new method is described in which the final product has a specific activity of one curie per milligram and contains less than three per cent damaged insulin.

Abstracted by John G. McAfee, M. D., The Johns Hopkins Hospital, Baltimore.

CAESIUM-134 IN MAN.

LIDEEN, K. & ANDERSON, I. Ö. *NATURE* **195**:1040, 1962.

On total body counting of Swedish Lapps, a gamma energy peak at 800 kev was encountered. This 800 kev peak was not found in the gamma ray spectra of Swedes from the Stockholm or Lund areas. There appeared to be a relation between this peak and the increased caesium-137 levels in people who eat reindeer meat in Northern Sweden. The 800 kev gamma peak was observed in samples of reindeer meat; the physical half-life was determined as 2.4 ± 0.5 years. The hypothesis that this nuclide was caesium-134 was confirmed by demonstrating the 605 kev gamma ray line of caesium-134 occurring in cascade with the 800 kev line by a gamma-gamma coincidence technique. The origin of caesium-134 in the biosphere is not known, as there is no known yield of this nuclide in nuclear weapons fission. An observation of caesium-134 in soil samples close to ground zero after an atomic balloon shot in Nevada has been previously reported. As caesium-134 is produced in reactors, reactor accidents might be the origin of this isotope in the biosphere.

The radiation dose to man from caesium-134 in the observed concentration is small. The radiation dose from caesium-137 is 57 millirads per year. An average caesium-134 content of 1.5 per cent of the caesium–137 level (the same ratio as in reindeer meat) contributes 1.3 millirads per year or only two per cent of the total radio-caesium irradiation dose.

Abstracted by John G. McAfee, M. D., Johns Hopkins Hospital, Baltimore.

CALENDAR OF EVENTS

Date	*Name of Course or Meeting*	*Place*
January, 1963		
7-18	Course in Medical Aspects of Radiological Health (201)	Rockville, Maryland USA
13-18	143rd Meeting of the American Chemical Society	Cincinnati, Ohio USA
23-25	2nd Technical and Scientific Congress of the German Atomic Forum	Munich, Germany
February, 1963		
11-22	Course in Basic Radiological Health (211)	Las Vegas, Nevada USA
19-22	Inter-American Conference on Radiochemistry	Montevideo, Uruguay
March 1963		
2-6	Annual Meeting of the Canadian Association of Radiologists	Quebec, Canada
April, 1963		
1-4	Annual Meeting of the American Radium Society	San Francisco, Calif. USA
11-13	Symposium on the Natural Radiation Environment	Houston, Texas USA
May, 1963		
	International Conference on the Sub-Cellular Radiobiology	San Francisco Bay Area, California, USA
June, 1963		
16-20	9th Annual Meeting of the American Nuclear Society	Salt Lake City, Utah USA
16-20	Meeting of the Section on Radiology of the American Medical Association	Atlantic City, New Jersey USA
9-14	8th Annual Meeting Health Physics Society	New York, New York
26-29	*10th Annual Meeting of the Society of Nuclear Medicine*	*Montreal, Canada*
July, 1963		
1-6	Conference on the Control of Cell Division and Induction of Cancer	Lima, Peru and Cali, Colombia
August, 1963		
9-15	6th International Congress of Nutrition, including Symposium on Balance Experiments and Isotopes in Nutritional Investigations	Edinburgh, Scotland
	3rd All-Union Radiation Chemistry Meeting	Moscow, U.S.S.R.
26-30	Symposium on Radiological Health and Safety in Nuclear Materials, Minning and Milling	Vienna, Austria
September, 1963		
	14th International Congress on Occupational Health	Madrid, Spain
October, 1963		
7-11	Symposium on Biological Effects of Neutrons Irradiations	Vienna, Austria
January, 1964		
	6th International Symposium on Radioactive Isotopes in Clinical Medicine and Research	Bad Gastein, Austria

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Hematologic Changes Observed Following I^{131} Therapy for Thyroid Carcinoma[1,2,3]

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INTRODUCTION

Although several reports describe a depression of circulating cellular elements in the blood in individual patients treated with I^{131} for thyroid carcinoma, (1, 2, 3) attempts to gain information concerning the incidence, duration and late effects on hematopoeiesis accompanying this type of therapy have been hampered by the poor prognosis in most reported series. Between 1947 and 1960, 200 patients received therapy doses of I^{131} (usually 100 to 300 mc) for thyroid carcinoma at the University of Michigan. During 1960 and 1961 a complete follow-up on all of these patients was attempted. An evaluation of the results of this therapy are the subject of a separate report. (4) In brief, 152 patients were re-examined, 45 were dead and only 3 were lost to follow-up. Of the 152 patients re-examined, 125 were clinically free of carcinoma, some of them as long as 12 years after initial treatment. In the course of routine treatment and follow-up, peripheral blood counts were obtained to assess the hematologic effects of this therapy. These blood counts have been studied in an attempt to determine; (1) the incidence of peripheral blood changes, (2) factors important in their induction, (3) their duration, and (4) possible adverse late effects.

MATERIALS AND METHODS

Patients. All patients were referred to the Clinical Radioisotope Unit for therapy of a pathologically diagnosed carcinoma of the thyroid gland. A total thyroidectomy was performed as the first step intreatment and following surgery

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[2]Presented at the 9th Annual Meeting of the Society of Nuclear Medicine, Dallas, Texas, June 29, 1962.

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the patient remained off thyroid medications for six weeks and then underwent a series of diagnostic studies including thyroid function tests, x-rays, I^{131} uptake, scintigrams and complete blood counts.

I^{131} Therapy. If concentration of I^{131} was found in the neck or other metastatic sites, a therapeutic dose of I^{131} was administered, usually in the amount of 100-200 millicuries. The patient remained in the hospital until the body content of I^{131} fell below 30 millicuries.

Follow-up. Following therapy the patient remained off thyroid, and diagnostic studies were repeated three months later. Treatment doses of I^{131} were given at three-month intervals until uptake was ablated or until the total dose of I^{131} became alarmingly large. The patient was then placed on replacement doses of dessicated thyroid (3 grains per day) and returned at yearly intervals for five years and then at five-year intervals thereafter (off thyroid for six weeks) for a repeat of all of the above diagnostic studies.

Blood Examination. Complete blood counts were performed in the hematology laboratories of the University Hospital and included a hemoglobin concentration, hematocrit, corrected sedimentation rate, white blood cell count, differential count and a platelet evaluation on the peripheral blood smear. The normal values for the hemoglobin concentration in males for this laboratory is 13.4 to

TABLE I

HEMATOLOGIC CHANGES AFTER I^{131} THERAPY FOR THYROID CARCINOMA

Status of Maximum Hematologic Changes After I^{131} Therapy	*Incidence*		*Etiologic Factors*				*Results of Therapy*	
	No. of Patients	*% Patients*	*Mean Tot. Dose I^{131}*	*Mean No. Treat. Doses*	*% Rec. X-ray Ther.*	*% Distant Metastases*	*% Survival*	*Mean Surv. Per.*
Normal Peripheral Blood	95	62%	145 mc	1.2	19%	14%	90%	4.2 yrs.
Subnormal Hemoglobin <12.2 gm female <13.4 gm male	54	35%	257 mc	2.0	41%	52%	87%	4.3 yrs.
Subnormal White Blood Ct. <4000 mm3	15	10%	332 mc	2.3	33%	40%	93%	4.5 yrs.
Subnormal Number of Platelet	5	3%	468 mc	3.8	50%	100%	80%	3.2 yrs.

17.6 grams per cent and for females 12.2 to 15.4 grams per cent. The normal white blood cell count is 4,000-10,000 cells per cubic millimeter (5).

RESULTS

Of the 200 patients, 159 (80%) had blood examined before and at least on one occasion after administration of I^{131}.

Incidence. The percentage of patients examined experiencing depression of the peripheral blood elements is shown in Table I. Of the 54 patients with subnormal hemoglobin concentrations, after treatment, only 5 had a significant anemia <10 gms%). The lowest hemoglobin observed in this series of patients was 6.6 gm per cent. The lowest WBC observed was 2000/mm^3. Of the 5 patients with platelet abnormalities, the abnormalities were described as "slightly decreased in 3 patients", "Moderately decreased" in one patient, and "markedly decreased" in one patient. In no patients were platelets absent. No bleeding was observed associated with platelet depression.

Factors Important in Inducing Depression of Peripheral Blood-I^{131} Dose. Abnormal peripheral blood findings were observed over a wide range of dosage of I^{131}. However, those patients with subnormal blood findings after therapy had received approximately twice the mean total dose of I^{131} as those who had consistently normal blood findings after therapy (Table I). Also, the mean dose necessary to cause leukopenia was higher than that resulting in anemia. The mean dose was higher still in those experiencing thrombocytopenia. In keeping with this higher dose, patients experiencing anemia and leukopenia received about twice the number of doses as those with normal blood findings and those who developed thrombocytopenia had received almost 4 times as many doses.

Preceding X-ray Therapy: About 25 per cent of the 200 patients treated received preceding external irradiation prior to the I^{131} therapy. Patients showing hematopoeitic depression had twice the incidence of preceding x-ray therapy as those who did not.

Widely Disseminated Metastases: Patients with a larger total mass of functioning metastases experienced a higher incidence of depression of circulating cellular elements in the blood than patients with a smaller total mass of metastasis. This was perhaps in part due to the fact that these patients received larger doses of I^{131}. However, of 12 patients with functioning distant metastases receiving less than 500 mc, 8 (75%) experienced blood changes, while of 36 patients receiving similar doses of I^{131} but with uptake apparently confined to the neck region, only 18 or 50 per cent, experienced depression of the blood count.

Results of Therapy. So far as could be determined, the hematopoietic side effects of I^{131} therapy did not influence the outcome of therapy in any way. (see Table I).

No difference was noted in patient survival time between groups of patients showing depression of circulating blood cells and groups of patients exhibiting no significant hematologic changes after treatment.

Duration. In general the abnormalities noted were of brief duration and not associated with symptoms.

The hemoglobin had returned to normal at least by the time of the one year

TABLE II

EXTENT AND DURATION OF HEMATOPOIETIC DEPRESSION FOLLOWING I^{131} THERAPY

	Interval After Completion of Therapy										
	3 Mo.	*1 Yr.*	*2 Yrs.*	*3 Yrs.*	*4 Yrs.*	*5 Yrs.*	*6 Yrs.*	*7 Yrs.*	*8 Yrs.*	*9 Yrs.*	*10 Yrs.*
Hemoglobin											
Number of Pts. Tested	75	59	43	28	15	15	14	4	5	2	1
Mean Hemoglobin Before Therapy	13.6	13.9	13.8	14.0	13.7	13.6	13.4	13.3	13.0	13.5	14.5
Mean Hemoglobin After Therapy	12.7	14.0	14.3	14.6	14.1	14.4	14.2	14.9	13.9	15.0	13.2
Degree of Change + Increase − Decrease	−0.9	+0.1	+0.4	+0.6	+0.5	+0.8	+0.8	+1.6	+0.9	+2.1	−1.3
p Value	.01	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
White Blood Count											
No. of Patients Tested	70	51	39	27	13	15	13	4	4	2	1
Mean WBC Before Therapy	7750	8150	7150	8050	7800	7250	8500	6650	4950	6900	
Mean WBC After Therapy	6600	6950	7600	8300	8000	7000	7800	7150	6650	5850	6650
Degree of Change + Increase − Decrease	−1150	−1200	+450	+250	+200	+250	−700	+500	+1700	−1100	
p Value	<.01	<.01	<.01	N.S.	N.S.	N.S.	N.S.	N.S.	<.01	N.S.	N.S.

follow-up after completion of therapy in all but eight patients. Of these eight patients, six were females in active menstrual life, and two were young men. Although this return to normal frequently occurred simultaneously with the administration of desiccated thyroid, in 3 patients the return to normal occurred while therapy was still in progress and the patient was myxedematous. The mean hemoglobin values at each follow-up interval are compared with the corresponding pretreatment hemoglobin values in Table II. The mean hemoglobin value fell significantly at the 3 months follow-up visit. Subsequently from the one year examination to 10 years after the completion of therapy there was no significant deviation from the pretreatment mean.

Leukopenia was a transient phenomenon and no leukopenia persisted over one year after the completion of therapy. In 5 patients the white count returned to normal while therapy was in progress and it was possible to give these 5 patients an additional mean dose of 265 mc without encountering further white blood cell depression. The mean white blood count at each follow-up interval is compared with the corresponding pretreatment value (Table II). Three months after completion of therapy there was significant decrease in the white blood count which continued through the one year follow-up. Subsequently, a significant increase in white count over pretreatment values occurred at two years and again at eight years after completion of therapy.

Thrombocytopenia was always transient and in no instance was of more than 1 years' duration. All 5 of the patients experiencing a decrease in platelet concentration had additional I^{131} therapy within 1 year (mean dose of 186 mc) without inducing recurrent platelet depression.

Differential Count: The changes which occurred in the differential count of the patients that experienced leukopenia are seen in Table III. The depression of white blood cells involved all elements. All of these counts were performed at least 3 months after treatment and thus the early lymphocyte depression described in earlier studies (1) was not seen. Instead a slight increase in the per

TABLE III

CHANGE IN DIFFERENTIAL COUNT IN PATIENTS EXPERIENCING LEUKOPENIA

	Total WBC	*Polymorphonuclear* %	*Ct.*	*Lymphocytes* %	*Ct.*	*Monocytes* %	*Ct.*	*Eosinophils* %	*Ct.*	*Basophils* %	*Ct.*
Mean Pre-treatment Count	5900	65	3853	24	1419	5	308	5	302	1	18
Mean Count at Maximum Depression	3100	61	1867	29	901	6	162	4	95	1	22
Mean Count after Recovery	5750	67	3982	24	1427	5	238	2	127	1	50

cent of lymphocytes was observed at the point of maximum depression of the white blood count.

Morphologic Changes: No specific alteration in the morphology of peripheral blood elements were observed in these patients before or after therapy. No instance of leukemia or aplastic anemia was observed in the 152 patients re-examined in 1960-1961. The death records of the 45 patients who had died were also investigated and no patient is known to have died of a blood dyscrasia.

DISCUSSION

Early studies of hematopoietic damage from radioactive iodine stressed the variable rate of radiation dosage and errors in the calculation of these doses. (1,2) Although these inaccuracies exist today, the study of a large group of patients given therapy doses of I^{131} does present some interesting trends.

Employing the method of treatment described in this paper, we have encountered a 36 per cent incidence of anemia, 10 per cent incidence of leukopenia, and 3 per cent incidence of thrombocytopenia. The abnormalities are related to the size and number of I^{131} doses in that those patients demonstrating abnormality have received twice the mean total dose and number of doses as those who have not. Although the induction of hypothyroidism no doubt plays a part in the production of these changes (particularly the anemia) the fact that the blood count of some patients returns to normal while the patient is still hypothyroid indicates the importance of the irradiation. Also as demonstrated by Sheline and Miller, (3) the bone marrow changes following I^{131} therapy in hypothyroid cancer patients are not those that ordinarily occur in hypothyroidism without thyroid cancer and I^{131} treatment. Other important factors in the production of blood changes disclosed by this study were the preceding administration of external x-ray therapy and the presence of large amounts of functioning distant metastases, both of which increase the delivered dose of ionizing irradiation to the body.

The blood changes noted in this study were brief in the absence of other complicating factors. Individual values for hemoglobin and white blood cells had returned to normal by one year after completion of therapy in practically all cases. Mean values for hemoglobin returned to pretreatment levels between 3 months to 1 year after completion of therapy and the mean white blood cell count returned to pretreatment levels between 1 year and 2 years after therapy.

There were no complications associated with these side effects in the management of these patients. In several instances additional I^{131} therapy was given in the face of blood changes without difficulty. There appeared to be no relation between prognosis and the presence of hematopoietic damage. We believe that the absence of serious hematopoietic damage may be attributed in part to the fact that an effort has been made to keep single doses of I^{131} below 200 mc and total doses below 800 mc in adults and 500 mc in children. The largest single dose administered in this group of patients was 276 mc and the largest total dose was 1142 mc. Only 5 patients received over 800 mc, and none of these 5 patients were freed of their disease by these large doses.

It is probable that keeping the I^{131} treatment doses a minimum of three months apart is important to allow time for some bone marrow recovery.

To date, we have not observed any blood dyscrasias such as leukemia or aplastic anemia in this group of patients. A longer follow-up will be required, however, to conclusively rule out any late delayed hematologic effects of irradiation.

SUMMARY AND CONCLUSIONS

1. Two hundred patients received therapy doses of I^{131} for thyroid carcinoma in the interval 1947 to 1960. Follow-up evaluations of the peripheral blood were made at three months and at yearly intervals up to ten years after completion of therapy in 159 patients.

2. The most common abnormality observed in the peripheral blood count after I^{131} therapy was a subnormal hemoglobin concentration seen in 36 per cent of the patients. Subnormal white blood counts were seen in about 10 per cent of the patients, and thrombocytopenia was seen in only five cases (3%).

3. These changes were roughly correlated with the total dose of I^{131} in that those who had blood abnormalities noted after treatment received about twice the mean total dose of those who did not experience abnormality. In addition, the extent of metastatic disease and the administration of preceding x-ray therapy were of importance in producing blood changes after I^{131}.

4. These changes were of brief duration, for the most part lasting less than one year, and were not symptomatic. No cases of leukemia or aplastic anemia have been observed to date.

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Long Term Experiences With the Use of P^{32} in the Treatment of Chronic Lymphocytic Leukemia[1]

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INTRODUCTION

Since 1936, when we introduced artificially-produced radioactive phosphorus (P^{32}) for the treatment of patients with chronic leukemia (1), we have had the opporunity to observe a large series of patients and their response to therapy. Some of these patients have survived for long periods after onset of the disease. The present report covers a larger experience than our previously recorded series of patients with chronic leukemia (2). Attempts are made to evaluate factors that may be used to predict long survival in chronic lymphocytic leukemia (C.L.L.) and to evaluate long-term effects of P^{32}.

One-hundred sixty-one patients with C.L.L. were studied during the period from 1936 to January 1960. Of these, 30 survived 10 or more years after the onset of symptoms or after diagnosis in asymptomatic cases (Long Survival Group, L.S.G.); 131 patients survived less than 10 years (Short Survival Group, S.S.G.). Twenty of the L.S.G. and 22 of the S.S.G. were living at the closing date, some of the latter might be expected to attain the L.S.G. The predominant treatment for patients in both groups was P^{32}.

DURATION OF DISEASE

Isolated instances of C.L.L. have been recorded with duration of the disease to 35 years after onset (3). Other instances of long duration have been documented (4-12). To our knowledge this series presents the largest number of patients with survival 10 or more years after onset who were treated with P^{32}. Table I presents the average duration of several reported series of C.L.L. These data are not completely comparable because definition of duration has been dated variously from onset of symptomatology or diagnosis. Because of similar statistical analysis, the series of Osgood and associates (13) and of Reinhard *et al.* (14) are comparable to the present study. Recency of the study representing im-

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[2]With the statistical assistance of Ellis Myers and Janice DeMoor.

provement in control of infectious and hemolytic complications, *vide infra,* may influence results. Thus, for prognostic use, these and other data must be suitably defined and qualified.

DESCRIPTION OF PATIENT POPULATION

All patients in the study were referred to us as having an established or a suspected diagnosis of C.L.L. Diagnosis was based on history and physical findings and confirmed by studies of blood and bone marrow. Only those whose disease process was considered chronic were included. No patients with a diagnosis of lymphosarcoma with subsequent development of leukosarcoma were included in this study.

TABLE I

A SERIES OF PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA WITH AVERAGE DURATION OF DISEASE

Author	*Date*	*Duration calculated from*	*Number of patients*	*Average duration (years)*
Minot et al. (5)	1924	onset symptoms	80	3.5
Leavell (8)	1938	onset symptoms	49	3.6
Wintrobe and	1939	diagnosis	23	1.07
Hasenbush (19)		onset symptoms	23	2.33
Wintrobe (15)	1939	onset symptoms	152	3.29
Bethell (31)	1942	onset symptoms	68	4.85
Pascucci (32)	1942	onset symptoms	64	2.8
Widmann (12)	1946	beginning treatment	24	3.3
Lawrence et al. (33)	1949	onset symptoms	100	4.5*
Diamond et al. (34)	1950	onset symptoms	53	4.2
Osgood et al. (13)	1955	total survival: spray roentgen treatment	23	5.2 (median)
		total survival: P^{32} treatment	140	4.2 (median)
Pisciotta and	1957	onset symptoms	21 (alive)	2.7
Hirschboeck (3)		onset symptoms	31 (dead)	4.0
Reinhard et al. (14)	1959	diagnosis	77 (dead)	3.5
			25 (alive)	6.5
This study	1960	onset symptoms	161	5.4 (median)
		diagnosis	161	4.4 (median)
		onset symptoms	42 (alive)	8.9
		diagnosis	42 (alive)	8.5
		onset symptoms	119 (dead)	5.3
		diagnosis	119 (dead)	4.6

*These patients are included in the present study.

TABLE II

SUMMARY OF PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA WITH DURATION LONGER THAN TEN YEARS

Patient	Sex	Age		Duration (years)			Early Findings								
		Onset Symptoms (S) Diagnosis (D)	Death	Onset symptoms	Diagnosis	D.L. Reg.*	Years after diagnosis	WBC X 10^3	Hb gm %	RBC X 10^6	Blood % lymphs	Bone marrow % lymphs	Spleen cm	Liver cm	Nodes (No. of groups enlarged)
R.D.	M	57.0 (D)			11.0	9.7	0.0	29.3	16.0	6.4	89	52	–	–	–
E.M.	M	56.0 (D)			14.0	10.8	3.0	133.0	11.0	3.4	93	93	tip	–	2
F.H.	M	51.0 (S)		13.0	12.0	10.8	2.4	300.0	12.8	3.75	98	76	3–4	–	3
H.W.	M	70.9 (S)	82.9	12.0	11.8	11.6	0.2	174.0	11.6	3.5	99	89	4	4	2
L.B.D.	M	70.0 (S&D)		10.7	10.7	10.3	0.4	32.8	13.9	5.2	79	42	2	2	3
V.B.	M	55.0 (S)	67.3	12.3	12.0	1.4	0.3	14.4	15.6	4.98	71	—	–	–	–
F.M.B.	M	55.0 (S)	66.0	11.1	10.9	8.7	0.2	39.2	11.6	5.01	94	†	8	–	3
J.R.	M	54.0 (S)		10.0	10.0	2.8	0.0	30.4	16.2	5.22	77	increased	–	–	2
F.E.	M	39.0 (S)	52.0	13.0	12.6	12.0	0.4	21.0	12.6	4.48	70	64	–	–	1
R.G.	M	53.0 (S)	64.0	11.0	11.0	7.6	3.5	42.5	15.0	4.38	91	75	3	3	1
G.B.	M	65.0 (S)	84.0	19.0	18.8	3.6	0.2	15.5	†	†	35	†	–	–	1
F.A.B.	M	39.0 (D)	54.0		15.0	13.9	0.0	148.0	11.9	†	96	89	–	–	3
E.B.	M	45.0 (S&D)		15.1	15.1	13.2	0.6	40.0	16.0	5.0	80	45	tip	1	2
W.H.M.	M	59.0 (D)			15.0	10.7	0.0	52.0	15.5	5.54	92	79	–	–	2
I.J.T.	M	38.0 (S)		16.7	16.0	16.0	0.8	54.0	15.7	5.29	76	55	–	–	3
G.S.	M	36.0 (S)		23.5	23.0	19.1	0.0	52.4	16.0	5.85	86	30	2	3	3
J.F.P.	M	35.0 (S&D)		23.3	23.3	18.4	0.0	21.5	10.2	3.1	90	45	–	–	3
T.B.	M	56.0 (S)		17.7	15.5	7.7	8.0	226.0	10.2	3.9	94	77	6	2	4
R.C.	M	58.0 (S&D)		17.0	17.0	7.8	10.0	214.5	11.9	3.9	97	88	–	–	–
L.P.D.	M	49.0 (S)	81.0	31.5	30.5	19.5	12.0	15.8	†	4.9	90	80	2	–	–
M.P.	F	59.0 (D)			19.0	18.8	0.1	92.4	12.4	5.56	81	55	4	–	–
H.S.	F	56.0 (S&D)	66.0	10.2	10.2	8.2	0.2	33.7	15.0	4.0	76	49	–	–	–
E.C.	F	55.0 (S)	67.0	12.0	10.0	8.9	0.5	65.0	13.7	4.97	82	increased	–	–	–
K.S.	F	66.0 (S)		10.0	8.0	7.4	0.0	20.0	11.8	3.93	60	28	–	3	4
A.D.	F	66.0 (S&D)		10.8	10.8	10.6	0.0	82.0	12.7	4.19	93	79	–	–	1
G.H.	F	59.0 (S)		11.5	11.3	11.5	0.3	24.5	11.8	3.92	85	48	–	–	–
L.C.	F	64.0 (S)		13.7	11.7	10.7	1.0	68.5	13.0	4.38	84	71	3	–	1
A.S.	F	68.0 (D)			13.1	9.9	0.0	245.0	12.1	4.46	89	63	tip	tip	2
M.S.	F	58.0 (S)		10.0	9.5	8.3	1.0	11.0	11.5	4.36	76	50	–	–	2
M.B.	F	60.0 (S)		14.8	14.5	14.5	0.0	13.1	12.3	3.6	78	43	–	–	–

TABLE II (Cont.)

TABLE II (Cont.)

Patient	Treatment			Findings at Death or Closing Date									Outcome
	P^{32} total mc	X-ray	Steroids or blood transfusions	Years after diagnosis	WBC X 10^3	Hb gm %	RBC X 10^6	Blood % lymphs	Bone marrow % lymphs	Spleen cm	Liver cm	Nodes (No. of groups enlarged)	
R.D.	—	—	steroids	9.3	31.4	17.7	4.95	76	79	—	–	1	Living; allergic bronchitis
E.M.	—	yes	—	13.7	24.0	11.9	4.58	†	†	—	–	–	Living; gout
F.H.	14.0	—	—	11.7	91.0	11.4	†	98	78	2	–	1	Living
H.W.	28.2	—	st & b.t.	10.6	47.2	13.4	4.39	95	79	7	tip	–	Died; pneumonia ca bladder
L.B.D.	—	—	—	10.0	9.0	10.5	4.1	42	†	—	–	–	Living
V.B.	14.9	yes	st & b.t.	10.0	200.0	4.5	1.4	96	97	10	–	3	Died; leukemic exacerbation
F.M.B.	16.9	yes	b.t.	10.8	17.2	9.9	3.05	91	increased	12	–	2	Died; pneumonia
J.R.	3.0	—	—	8.0	59.4	14.0	5.22	89	75	—	3	–	Living; prostate surgery
F.E.	11.7	yes	—	12.6	15.0	15.8	5.58	58	26	4	4	1	Died; cerebral thrombosis
R.G.	1.0	—	—	10.0	5.2	†	4.0	62	†	4	–	–	Died; presenile brain
G.B.	21.0	—	—	18.6	23.2	8.5	3.4	67	80	2	–	2	Died; senility
F.A.B.	90.0	yes	—	15.0	183.0	8.8	3.0	99	94	—	–	–	Died; pneumonia
E.B.	83.5	yes	—	12.0	158.0	14.2	†	98	63	6	2	–	Living
W.H.M.	30.0	yes	—	15.0	3.2	11.5	3.9	28	18	—	–	1	Living; ASHD
I.J.T.	73.8	—	st & b.t.	15.1	10.4	13.1	3.7	88	87	tip	–	1	Living; hemolysis
G.S.	26.0	—	—	22.0	8.7	14.8	5.4	41	52	tip	–	–	Living
J.F.P.	10.0	yes	—	23.3	11.0	15.0	4.9	83	74	—	–	1	Living
T.B.	44.5	—	b.t.	15.7	23.9	10.6	3.3	96	99	8	2	1	Living; hypogammaglobulin
R.C.	19.0	yes	—	17.0	147.0	14.8	5.1	99	95	4	–	–	Living
L.P.D.	23.5	yes	—	30.0	19.1	14.2	3.8	80	80	—	–	–	Died; ca sigmoid, ca prostate
M.P.	27.6	yes**	—	13.0	58.7	10.2	3.8	50	62	—††	‡	2‡	Living; ca breast
H.S.	4.0	yes	st	10.2	14.4	12.5	4.5	50	63	—	‡	–	Died; ca endometrium
E.C.	6.6	—	—	9.0	14.7	14.2	4.8	51	†	†	†	†	Died; coronary occlusion
K.S.	13.0	—	—	7.2	15.1	12.0	4.7	55	15	8	11	4	Living
A.D.	35.0	—	—	10.8	129.0	10.4	3.1	99	91	—	–	1	Living
G.H.	—	—	—	9.2	28.9	13.0	4.3	83	41	5	tip	–	Living
L.C.	4.0	—	—	10.2	83.5	12.5	†	95	78	4	–	1	Living
A.S.	10.0	—	—	13.0	57.7	12.2	4.0	80	†	6	†	†	Living
M.S.	8.5	—	st	9.5	10.2	10.9	3.3	86	89	—	–	–	Living; hemolysis
M.B.	39.4	—	st	14.5	107.0	11.3	3.5	96	82	12	–	–	Living; hemolysis

*Donner Laboratory Registration
†Followed elsewhere—data not available
–Absent or none
**For carcinoma of breast
‡Carcinomatous metastases
††11 months after closing date

All patients were Caucasian, except two Negro males in the S.S.G. Males totaled 109 patients or 68 per cent; females totaled 52 patients or 32 per cent, the usual sex ratio for this disease (15). In the S.S.G. there were 89 males, 68 per cent, and in the L.S.G. there were 20 males, 67 per cent. Median age to the nearest birthdate at onset of symptoms was 56 years and at diagnosis, 57 years for both groups. At Donner Laboratory, the median age for the S.S.G. was 57 years and for the L.S.G. it was 59 years. Minot and Isaacs (5) estimated that in 72 cases of C.L.L. a 9-month period elapsed between the onset of symptoms and the diagnosis. In our series, the interval between onset of symptoms and establishment of diagnosis for the group surviving 10 years or more ranged from 0 to 2.2 years, with a median interval of 0.2 years.

Table II presents a summary for the patients of the L.S.G. with ages at onset, duration in years from onset of symptoms or diagnosis or both, hematologic and physical findings at the time of registration and just prior to death or closing date, treatment and outcome. Similar data for the S.S.G. are not presented owing to limitation of space.

SURVIVAL STATISTICS

The hazards of estimation of onset data have been presented by Dameshek and Gunz (16). They suggest, "It is probably best to determine as accurately as possible, in the particular circumstances, the 'total' duration, as well as that from the beginning of treatment, and the value of published series is increased where both figures are given". We have calculated for each patient in this study the duration from 1) onset of symptoms that might be related to leukemia, 2) date of diagnosis on basis of physical and hematologic findings, and 3) date of first visit to us.

It is unfortunate that no standard statistical method for survival has been adopted for studies such as the present one, in which the patient group includes living patients as well as deceased. Tivey (17) developed concise criteria for statistical evaluation of therapy. The uncomplicated method of Best and Limarzi (18), by which survival data of this series have been calculated, answers all of Tivey's criteria for analysis of duration of disease. At the median survival 50 per cent of the patients are dead.

Figure 1 presents survival curves and median survival times, given in parentheses, for the entire series from onset of symptomatology (5.4 years), from diagnosis (4.4 years), and from Donner Laboratory registration (2.4 years). The curves shown represent straight-line fits of the data following log-normal transformations. Percentages of patients surviving 5 years after the respective reference points in time were 68.9, 59.5, and 32.9 per cent. Comparable percentages for 10-year survival were 21.6, 20.4, and 12.9 per cent.

Fifty per cent survival from date of Donner registration between the 10-year periods 1938-1947 and 1948-1957 were 1.35 years and 3.35 years, respectively. Pneumonia was the terminal event for 30.2 per cent of the group dying before 1948 and for 22.7 per cent of the group dying after 1948. There was no marked difference between the percentages of the two groups for death directly related to hemorrhage, anemia, or uncontrolled leukemic involvement; whereas 18.2 per

cent of the late group (since 1948) died as a result of coronary disease or its sequelae, only 7 per cent of the early group died with this complication. These data would lend support to the assumption that among other factors, antibiotics (not in widespread use before 1948) have aided in increasing life expectancy in this chronic disease. Especially is this true for the early course of the disease before extensive involvement has occurred.

PRESENTING SYMPTOMATOLOGY

It has been stated that if leukemia is discovered accidentally in the absence of symptoms, periods of 2 to 5 years may elapse before symptoms are noted (19). In our study, only 7 per cent (9 patients) of the S.S.G. had no symptoms prior to diagnosis, whereas 20 per cent (6 patients) of the L.S.G. were asymptomatic prior to diagnosis. Of the latter group, symptoms developed within 6 months to 8 years (average 2.4 years) after diagnosis was made.

Multiple symptoms was the usual finding for those having symptoms, with fatigue, weakness, and dyspnea common concurrent complaints. All symptoms were more frequent for the S.S.G., except pain which was present in 19 per cent of the L.S.G. and in 12 per cent of the S.S.G. It is of note that in the S.S.G. 29 per cent complained of dyspnea and 8 per cent, enlargement of abdomen, while

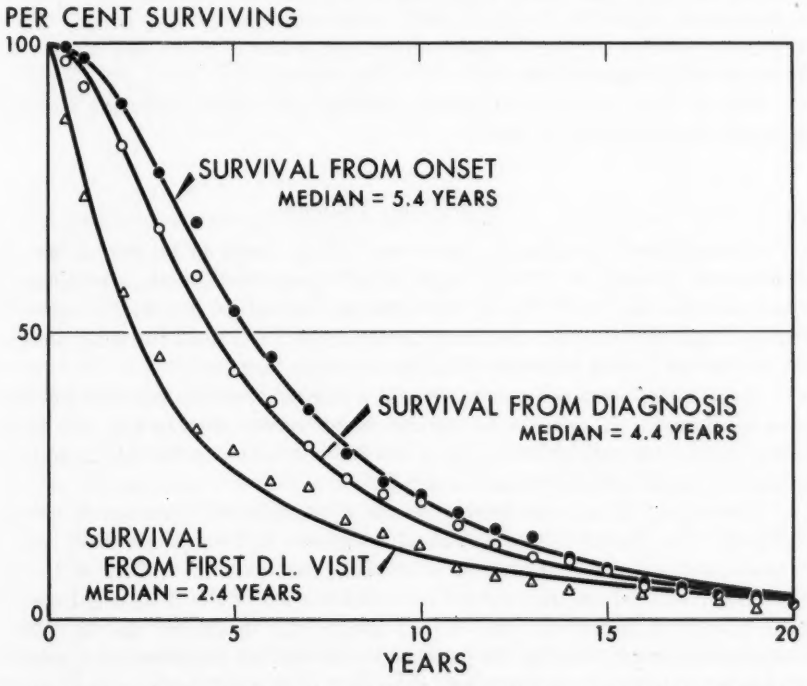

Fig. 1. Survival curves for 161 patients with chronic lymphocytic leukemia with median survival times from onset of symptoms, diagnosis, and from first Donner Laboratory visit.

none of the patients in the L.S.G. had these as early symptoms. Complaints of enlarged lymph nodes and hemorrhagic phenomena were noted by 20 per cent of the S.S.G. and about 5 per cent of the L.S.G. Fever was not an outstanding symptom of either group.

PHYSICAL FINDINGS

Early physical findings, including size of spleen and liver and enlargement of nodes, were recorded. In the L.S.G. spleen was enlarged in 43 per cent, liver in 27 per cent and nodes in 70 per cent. Corresponding figures for the S.S.G. were 63, 44 and 80 per cent respectively. In addition to the less frequent occurrence, the degree of organ enlargement was less in the L.S.G. Only 2 of the 13 L.S.G. patients with palpable spleens had splenic enlargement more than 4 cm below the left costal margin, whereas 64 per cent of the S.S.G. having splenic enlargement demonstrated this degree of enlargement. Three or more groups of lymph nodes, i.e., cervical, axillary, and inguinal, were enlarged originally in 43 per cent of the S.S.G. and in 27 per cent of the L.S.G., while comparable figures for the two groups in whom no lymphadenopathy was found were 20 and 30 per cent.

Late physical findings in the L.S.G. showed splenic sizes increased in twelve patients; an equal number were unchanged from the early findings; and 6 showed a decrease in size. On the other hand, node enlargement was greater in only 4 of these patients 10 years or more after onset, while in more than 50 per cent, nodes were decreased in size.

For the S.S.G. there was a greater tendency for spleen and node size to be increased in the follow-up period.

LABORATORY FINDINGS

Hemoglobin determinations were more often found to be low at the time of diagnosis in the S.S.G. Twenty-eight of this group had less than 10 grams per cent, whereas none of the L.S.G. had levels in that range. It is highly significant that hemoglobin values for the first quartile of the S.S.G. (4.9 to 10.2 g per cent) fell below the lowest value for the L.S.G. (10.2 g per cent).

Total white blood cell counts showed a marked variation for both groups at time of diagnosis. There was no significant difference between the two groups. White cell values ranged from 5000 to 780,000 per cu mm in the S.S.G. and from 11,000 to 300,000 per cu mm in the L.S.G.

The degree of marrow lymphocytosis at the time of diagnosis is given in Table III. For the S.S.G., an additional 5 patients had diagnostic bone marrow examinations revealing an excess of lymphocytes, but the differential counts were not available. Another patient had confirmation of the diagnosis by a later bone marrow examination. One of this group was diagnosed on the basis of lymph node biopsy, leaving 31 patients for whom the diagnosis was based on peripheral lymphocytosis with physical findings of enlarged nodes, spleen or liver or both. There were four patients of the S.S.G. with non-diagnostic bone marrow differentials showing less than 30 per cent lymphocytes at initial examination.

However, of these 4, lymph node biopsy was diagnostic for the patient with a 16 per cent marrow lymphocytosis; repeat marrow examinations of two patients showed over 40 per cent lymphocytes; the remaining patient, with marrow lymphocytosis of only 28 per cent, had no significant enlargement of nodes, spleen, or liver, but white cell counts have consistently been above 25,000 per cu mm with 70 per cent or more lymphocytes on differential blood count.

TABLE III

PERCENTAGE OF LYMPHOCYTES IN INITIAL BONE MARROW EXAMINATION

	Short survival group	*Long survival group*
Number of patients	92*	25**
Range	16.5 to 99	28 to 93
Mean	86	63
Median	77	63
First quartile	16 to 58	28 to 45
Second quartile	60 to 77	48 to 63
Third quartile	78 to 86	64 to 79
Fourth quartile	86 to 99	79 to 93

An additional 5* and 2** patients had diagnostic bone marrow examinations at time of diagnosis but no differential count was available.

METHOD OF TREATMENT

The primary method of treatment was radioactive phosphorus (P^{32}); however, some patients received both P^{32} and local X-radiation therapy to lymph nodes or spleen. Only a few patients additionally received an alkylating agent. Summary of treatment for the two groups is given in Table IV. Unlike the practice of Osgood and associates (13), we institute treatment *only* for specific indications such as splenomegaly, lymphadenopathy, anemia, and lymphcytosis in which there is progression of symptoms attributable to the disease (2,104,20). We believe that asymptomatic patients do not need therapy.

Single courses usually consisted of 4 to 6 injections of P^{32} at weekly intervals, with total dosages amounting to 3 to 8 mc. The efficacy of therapy was judged by improvement in symptomatology, decrease in splenomegaly or lymphadenopathy, or both, decrease in white blood cell count, and improvement of hemoglobin, hematocrit, and red cell counts. The interval between courses of therapy varied considerably.

Five of the S.S.G. and 2 of the L.S.G. received no specific therapy for the leukemic process. Radioactive phosphorus alone was used to treat 39 of the former group and 11 of the latter group; while P^{32} was given in conjunction with X irradiation, steroids, or both to an additional 62 and 14 patients. Overall dosages of P^{32} from start of therapy to death or closing date compared closely for both

groups and ranged from 0 to 79.8 mc in the S.S.G. and 0 to 90 mc in the L.S.G. Because the latter group has been followed for a longer period (10 years and over) this indicates less total treatment during duration of disease. Treatment rates per year were extremely variable in both groups and depended upon activity of disease *(vide supra)*. A few of the patients received whole-body spray radiation, while others were treated with conventional X-radiation delivered to enlarged nodes or spleen or both.

Adrenal cortical steroids were used at one period of time for 23 of the S.S.G. and for 7 of the L.S.G. These drugs were used primarily to treat patients with hemolytic processes or rapid exacerbation of the leukemic process. Anemia was a frequent finding in the S.S.G. as noted by necessity of blood transfusions in 72 patients (55 per cent), whereas only 5 of the 30 L.S.G. (17 per cent) required blood transfusions.

Testosterone, in the form of sublingual tablets, was given in dosages varying from 6 to 8 mg for intermittent periods or continuously to about one-third of all patients. We have been using testosterone in this way during the past 15 years and noted (20) an increased sense of well-being in the majority of subjects, as well as an increase in red cell volume, hemoglobin, and hematocrit (21). Further

TABLE IV

SUMMARY OF TREATMENT

	Short survival group (number)	*Long survival group (number)*
No P^{32}, X-ray or steroids	5	2
P^{32} alone	39*	11
X-ray alone	11+	2
Steroids alone	0	1
X-ray and P^{32}	52#	8**
P^{32} and steroids	10++	4
X-ray and steroids	2	0
X-ray, P^{32} and steroids	10##	2
TEM and steroids	1	0
Y^{90} alone	1	0
Total	131	30
Transfusions	72	5

Additional Treatment:

*1 had Y^{90}

+2 had Y^{90}, 1 Sr^{89}, 1 TEM and chlorambucil, 1 urethane

#2 had urethane, 1 Sr^{90}, 3 Y^{90}, 2 TEM, 1 chlorambucil, 1 6-MP

**1 had X-ray for breast carcinoma

++1 had 6-MP

##1 had TEM, 1 chlorambucil

work is underway. It is impossible to evaluate any direct effect of androgen on suppression of the leukemic process as suggested by animal studies (22) because most of these patients received concomittantly some form of therapy directed to control of leukemia. The apparent improvement in the level of the red cell counts in many patients after testosterone therapy is not easily explained. More recently, Gardner and Pringle (23) have found androgen therapy to be helpful in improving anemia in patients with hypoplastic anemia, myeloid metaplasia, and malignant reticulum diseases (multiple myeloma, lymphatic leukemia, and Hodgkin's disease). They suggested that the increased proliferation of erythroid precursors points to expansion of the bone marrow stem cells as the primary effect. Patients with refractory anemia associated with thymoma have responded to androgen therapy (24). Petrakis (25), using diffusion chamber techniques, has shown that autologous or homologous leucocytes, implanted in guinea pigs treated with a single injection of 50 or 100 mg of long-acting androgen (testosterone ethinate), develop into normoblasts. Maximal normoblastic development occurred within three weeks and continued for another week with a subsequent "petering out."

COURSE OF THE DISEASE

The non-homogeneous nature of this disease has been previously pointed out (2, 14, 15) and three basic patterns (3) have been suggested: 1) stationary or slowly progressive; 2) progressive symptoms with increasing size of nodes, liver, and spleen; and 3) development of hemolytic anemia.

With reference to group 1, as in the case of patients with cancer, some patients seem to have a relative resistance or immunity to the disease. The recently advanced clonal-selection theory of immunity (26) postulates that the action of the antigen is simply to select for proliferation that particular clone of cells that can react with it. Perhaps in the effective treatment of C.L.L. with P^{32} or with external radiation, the antigenic determinants or the antibody-producing cells are altered in certain instances. Some of our earlier work on lymphomatous mice (27) treated with P^{32} showed a small percentage of cures, possibly due to the development of immunity during P^{32} therapy.

We have noted also that any one individual patient may suddenly or slowly change from a steady state to a rapidly progressive pattern. Also, the development of hemolysis may interrupt either a slowly progressive pattern of many years duration or may occur soon after onset in a more rapidly progressive disease pattern.

It is to be anticipated that a few of the 22 surviving patients in the S.S.G. may ultimately reach the L.S.G. as some of these show a slowly progressive pattern and may be predicted to fall with the L.S.G. However, S.S.G. who are now deceased had a definitely more severe course than the L.S.G. with regard to anemia, frequent infections, and leukemic involvement of organs. On the other hand, the prevalence of hemolytic complications was only 8 per cent (10 patients) in the S.S.G. as compared with 17 per cent (5 patients) in the L.S.G. In the S.S.G., hemolysis was detected at onset in one patient, within 1 year in 4 patients, and within 2 to 4 years after diagnosis in 5 patients. Five patients of the L.S.G. developed hemolysis 8.5 to 12 years after diagnosis or terminally. It

is reported that about one-third of patients with C.L.L. develop hypogammaglobulinemia during the course of their illness (28). However, routine serum protein electrophoresis has only been routinely used within the past few years and many of our patients in our series died previous to this. One patient in the L.S.G. was found to have this complication. Patient T.B. of the L.S.G. developed recurrent debilitating respiratory infections 8 years after the diagnosis of C.L.L. was made. Hypogammaglobulinemia was confirmed by protein electrophoresis and adequate treatment was instituted. In the year and a half since that time, infections have not occurred except once when the gamma globulin injection inadvertently was not given.

EFFECTS OF RADIATION

Since our first use of artificially-produced isotopes to treat patients in 1936, we have paid particular attention to the evaluation of the patient's course of illness and cause of death to determine whether treatment resulted in the induction of acute leukemia or other delayed effects. Despite the large dosages of P^{32} used to treat the majority of patients included in this series of 161 cases, no instances of the development of acute leukemia were encountered. Follow-up studies on living patients and autopsy data showed that the observed occurrence of malignancies in our series was no greater than that reported in the literature for leukemic patients and no greater for patients already having one form of cancer. In the 2829 autopsied cases of malignancies studied by Warren and Ehrenreich (29), the observed incidence of multiple tumors (1932-43) was 68 per thousand or 11 times the number expected if chance alone were a factor. They reported 97 autopsied cases of leukemia of which 11 showed multiple malignant neoplasms. It can be assumed that none of these cases was treated with P^{32} because it was not avaliable for general use at the time of their study. In the present series of 161 cases in which 9 patients developed carcinoma, other than of skin or lip, 3 had no radiation, 5 had received from 2 to 22.6 mc of P^{32}, and 1 had been treated with two series of roentgen rays to the spleen prior to the onset of carcinoma. It would appear that chronic leukemia is associated with an increased susceptibility to malignancy as are other neoplasms, but that this susceptibility is not caused by radiation or isotope therapy. Thus it appears that with the large therapeutic doses of radioisotopes we have given over many years, no cases of acute leukemia were observed nor was there an increase in the incidence of multiple neoplasms. Cronkite recently reviewed the adequately-documented cases of leukemia attributed to radiation exposure occurring from 1911 to 1959 and found this to total the surprisingly small number of 226 cases (30).

CAUSES OF DEATH

Table V presents the causes of death for the 119 deceased patients of the series. Autopsy data were obtained from 51. Causes of death for the remainder were determined by the terminal clinical manifestations. Absolute certainty of which of several contributing factors actually caused death was impossible in some instances. Death was due directly to chronic lymphocytic leukemia, to hemorrhage, or to bacterial pneumonia in 65 per cent of the deceased S.S.G.

and in 40 per cent of the deceased L.S.G. Not unusually, the course of these patients is characterized by an increasing degree of lymphocytic infiltration of the bone marrow, leading to more and more severe anemia, in spite of P^{32} therapy continued in doses insufficient to suppress the platelet count below 50,000 per cu mm. The transfusion reaction, resulting in death of one patient, occurred during surgery for hip fracture and cannot be directly related to the anemia

TABLE V

CAUSES OF DEATH OF 119 PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA

	Short survival group		*Long survival group*	
	(number)	*(%)*	*(number)*	*(%)*
Death due directly to leukemia	35	32.2	1	10
Uncontrolled involvement	16	14.6	1	10
Hemolysis, uncontrolled	1	1.0		
Hypersplenism	1	1.0		
Cachexia	1	1.0		
Anemia	12	11.0		
Toxemia (?) etiology	4	3.6		
Pneumonia, bacterial	27	24.8	3	30
Hemorrhage	9	8.3		
Cerebral	4	3.6		
Gastrointestinal	3	2.7		
Pulmonary	1	1.0		
Generalized	1	1.0		
Transfusion reaction	1	1.0		
Cardiac disease	16	14.6	1	10
Acute myocardial infarction	13	11.9	1	10
Acute pulmonary edema	3	2.7		
Carcinoma	2	1.8	2	20
Acute appendicitis, ruptured	1	1.0		
Postoperative, leg amputation	1	1.0		
Postoperative, mastoidectomy	1	1.0		
Cerebral thrombosis			1	10
Presenile brain disease			1	10
Senility			1	10
Accidental	1	1.0		
Unknown	15	13.7		
Total	109	100	10	100

associated with leukemia. Carcinomatous metastases from endometrium and pulmonary embolus associated with carcinoma of the sigmoid colon were the causes of death of 2 of the L.S.G. Lung and pancreatic metastases resulted in death of 2 of the S.S.G.

SUMMARY AND CONCLUSIONS

A series of 161 patients with chronic lymphocytic leukemia, 30 (18.6 per cent) of whom have survived from 10 to 31 years after onset, has been presented. Twenty of these long-survival group patients are still living. Survival times have been calculated from 1) onset of symptomatology or diagnosis in asymptomatic cases; 2) diagnosis; and 3) first visit to Donner Laboratory.

1. Analysis of symptomatology, physical findings and laboratory data at the time of diagnosis for the 2 groups indicates that there is no absolute measure for prognosis. The important conclusion from this study re-emphasizes the fact that the diagnosis of C.L.L. can be compatible with many years of useful life and should bring reassurance to both doctor and patient that the disease follows a relatively benign course in an appreciable number of cases.

2. Therapy was primarily with P^{32}. No cases of acute leukemia were observed nor was the incidence of malignancies increased as a result of treatment. No other sequelae were encountered that would contraindicate the use of radiation.

3. Pneumonia as a cause of death was significantly higher for the group dying before 1948, while for the same interval coronary disease or its sequelae was responsible for death in a percentage less than half that of the later period.

4. While hemolytic complications may develop at any stage of C.L.L., they tended to occur more frequently in those patients in whom the course had been long and slowly progressive.

5. Subjective and objective improvement occurred in those patients treated with oral androgens. Further work is indicated to associate a direct leukemic suppressive effect.

6. Comparison of future studies would be facilitated if survival statistics are determined by some method similar to that used in this series.

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Use of the Radioisotope Renogram in the Differential Diagnosis of Renal Insufficiency Following Vascular Surgery[1]

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Houston

Within the past decade the surgical therapy of numerous disease processes involving the aorta and its major branches has become well established. Resection of the involved segment of the aorta with graft replacement is the procedure of choice in the management of aortic aneurysms. (1, 2) Numerous bypass procedures and technics of direct attack are commonplace in the therapy of atherosclerotic occlusive lesions of the aorta and iliac arteries, the mesenteric vessels, and the renal arteries. (3-7) The risk associated with these procedures has been reduced considerably in recent years. Occasionally, however, an otherwise successful surgical procedure is complicated by the development of renal insufficiency.

Expeditious determination of the etiology of the occasional case of renal insufficiency is a prerequisite for the successful management of such a patient. The renal arteries may have become occluded by athermatous material, or dissection into or of the renal arteries may have resulted in thrombosis of these vessels. An unrecognized transfusion reaction may have occurred during surgery, or ureteral obstruction may have been produced accidentally during the procedure or during closure of the posterior parietal peritoneum. Immediate operation is mandatory in several of these situations. However, if renal insufficiency is secondary to a transfusion reaction, additional surgery is contraindicated.

Translumbar or retrograde aortography may be employed to visualize the renal arterial circulation, but these procedures impose certain problems and hazards in the postoperative patient with renal insufficiency. General anesthesia, if employed, and the nephrotoxic effects of the contrast medium may produce

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untoward effects. (8) A rapid, simple and safe technic for determining the cause of renal insufficiency in these patients would add much to their successful management.

Lebretti, O'Connor and Grayhack (9, 10) reported that the radioisotope renogram was helpful in differentiating the various causes of renal insufficiency developing after non-vascular surgery. Since this procedure does not impose further trauma to the patient, and allows for an accurate estimation of various phases of renal function, it would appear to be an ideal method for differentiating between the possible causes of renal insufficiency following surgery on the aorta and its major visceral branches. To determine if the radioisotope renogram could be used for this purpose, the following study was performed.

MATERIALS AND METHODS

Fifty-six mongrel dogs, varying in weight from 10 to 25 kg, were anesthetized with pentobarbital sodium. Normal renogram patterns were determined and each animal was used as its own control. The animals were divided into three groups to simulate the three major clinical situations associated with renal insufficiency following vascular surgery—renal artery occlusion, transfusion reaction, and bilateral ureteral obstruction.

Group 1 consisted of animals in which renal artery occlusion was simulated by doubly ligating the renal arteries. In those animals in which only one renal artery was ligated, urinary bladder catherization was found necessary to prevent erroneous tracings secondary to the accumulation of radio-active urine in the bladder. Due to the small size of some of the animals in relation to the size of the renogram probes cross-monitoring of the contralateral kidney occasionally occurred when only one renal artery was ligated. In order to circumvent these difficulties, both renal arteries were doubly ligated through a midline abdominal incision. Following closure of the incision, renograms were repeated. Complete ligation of both renal arteries and any accessory renal vessels was confirmed by autopsy after sacrifice of the animals.

Group 2 consisted of those animals in which a transfusion reaction was simulated. As renal ischemia or prolonged hypotension might produce changes in the kidney different from those occurring with a transfusion reaction, a modification of the method of Mueller and Mason (11) was employed. Although such a method does not produce a reaction exactly comparable to a clinical transfusion reaction, it was believed that this method more closely approximated the clinical situation than other experimental methods of producing renal insufficiency in animals.

Two to three weeks following the administration of 50 ml of human whole blood intravenously, the dogs were anesthetized and discrete renal function studies were performed. Glomerular filtration rate and renal plasma flow were determined using inulin and para-aminohippurate. These methods and technics have been described previously. (12) Control renograms were then obtained. A sham operation was performed, opening the abdomen through a midline incision and exposing both renal arteries, after which the incision was closed. During the operative procedure 100 ml of the same type of human whole blood which the

animal had received previously was given intravenously. Renal function determinations and renograms were repeated. Upon completion of the experiment the animals were sacrificed and the kidneys were examined grossly and microscopically.

Group 3 consisted of animals in which bilateral ureteral obstruction was produced. Following anesthetization both ureters were exposed through a midline abdominal incision and doubly ligated. The incisions were closed and renograms were repeated.

Renograms were performed with the animals in the supine position by angling the detectors under the anterior ribs so that they were in close approximation to the kidneys. The 2 inch scintillation crystals were recessed one inch within cylindrical columators which were one inch thick. The shields were held in apposition throughout their length so that the distance between the crystals were kept at a minimum. The crystal edges were thus 2 inches apart. Scintillation detectors were connected to linear ratemeters which in turn drove milliamp recorders with a chart speed of 12 inches per hour. Approximately 40 μc of I_{131} ortho-iodohippuric acid was used for each test. Pulse height analysis was not used.

The actual dose needed for technically adequate curves was determined by giving a test dose, using a scale factor of 30K counts per minute and allowing the kidneys approximately five minutes to concentrate this dose. The detectors were then adjusted to a point of maximum counting rate. The height reached by the test curve was used to calculate a dose which would bring the renogram curve high on the 300 K scale without going off scale as the kidney concentrated the tracer dose. The scale factor was changed to 300 K, and the background radioactivity from the test dose was removed from the record by adjusting the zero or baseline control. An intravenous infusion of 5 per cent dextrose in distilled water was started prior to injecting the tracer dose. This infusion was run at a slow rate since a high infusion rate will shorten the excretory phase making the curves difficult to interpret. The tracer dose was injected through the intravenous tubing fast enough to make it appear on the record as an instantaneous injection. The records were run for 20 minutes or until the curve reached 50 per cent of the peak height. The ratemeter scale factor used was 300,000 counts per minute with an integration constant of 0.5 seconds. Prior to the second or post surgical renogram, the detectors were repositioned as they were for the control renogram. Any residual radioactivity was removed from the record by changing the zero control. When this is done with the ratemeters used, the effective time constant decreases making the second tracing appear wider than the control.

One clinical case of acute renal insufficiency following aortic vascular surgery was available for study. This patient excreted only minimal amounts of urine following operation and expired as the result of a myocardial infarction on the second day after surgery. At autopsy the renal vascular tree was found to be intact, but the kidneys demonstrated typical changes of "lower nephron nephrosis". A renogram was performed on the day following operation.

Our technic of performing renograms in humans using portable equipment

is the same as that described for the experimental studies, except for the positioning of the detectors. The kidneys are located by the areas of maximum radioactivity following a test dose of the isotope or by a roentgenogram of the abdomen. The detectors are placed directly over these areas, the radioisotope injected through the tubing of an intravenous infusion, and the tracing obtained.

RESULTS

Group 1 consisted of 26 animals from which 3 were discarded after autopsy demonstrated that an accessory artery to one or both kidneys was still intact. Another animal was discarded because a portion of the radioisotope dose was injected outside of the vein. Four animals studied prior to the use of urinary bladder drainage were discarded, and 18 animals remained in the group for analysis.

Figure 1 demonstrates the type of tracing obtained with unilateral renal artery ligation in a large animal. Following the arterial spike, the tracing on the left (ligated) side showed no concentration of the radioisotope and appears similar to a blood curve. On the right (un-ligated) side there was a relatively normal renogram pattern. This type of tracing was seen in 4 of the 12 in which unilateral renal artery ligation was performed. Figure 2 demonstrates an equivocal type

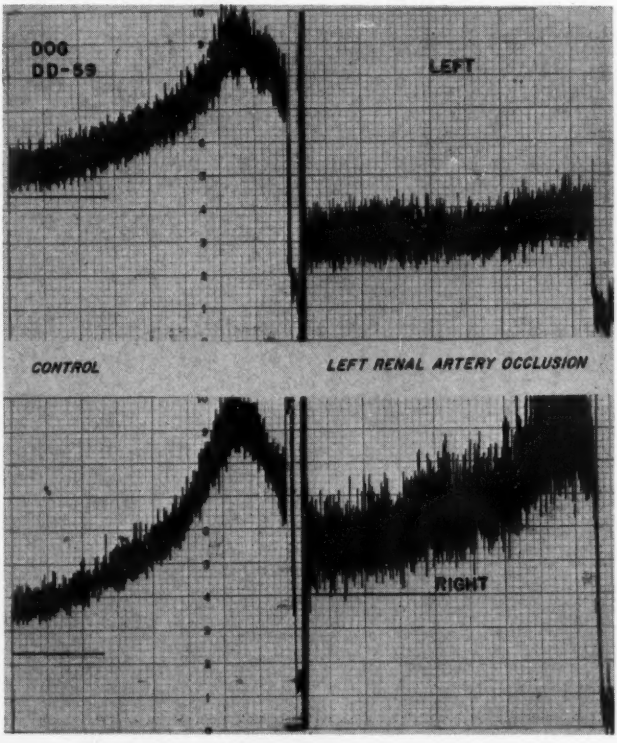

Fig. 1. Renograms before and after left renal artery occlusion demonstrating no concentration of radioisotope by the left kidney following ligation.

of tracing which was obtained in the other 8 animals in which only one renal artery was ligated. This tracing cannot be differentiated from those seen following a transfusion reaction, due to cross-monitoring the right (un-ligated) kidney by probe over the left (ligated) kidney in these small animals. In the anuric human in whom neither kidney is functioning, similar difficulties should not be encountered.

Figure 3a and 3b demonstrate the typical type of renogram obtained in all 6 animals in which bilateral renal artery ligation was performed. Following an arterial spike no renal concentration of the radioisotope was seen. These curves demonstrated total absence of functioning renal parenchyma and were identical to blood curves. As only bilateral renal artery ligation simulated the clinical situation seen with bilateral renal artery occlusion and anuria, it would appear that a distinctive renogram pattern was present in this group.

Group 2 consisted of 26 animals in which transfusion reactions were simulated. Ten of these sensitized dogs became dyspneic and hypotensive, followed by respiratory arrest and death immediately after the second transfusion of human whole blood and appeared to have experienced an anaphylactoid reaction. In 7 of 16 surviving animals no significant change in renal function occurred, as measured by glomerular filtration rate and renal plasma flow. Similarly, no change

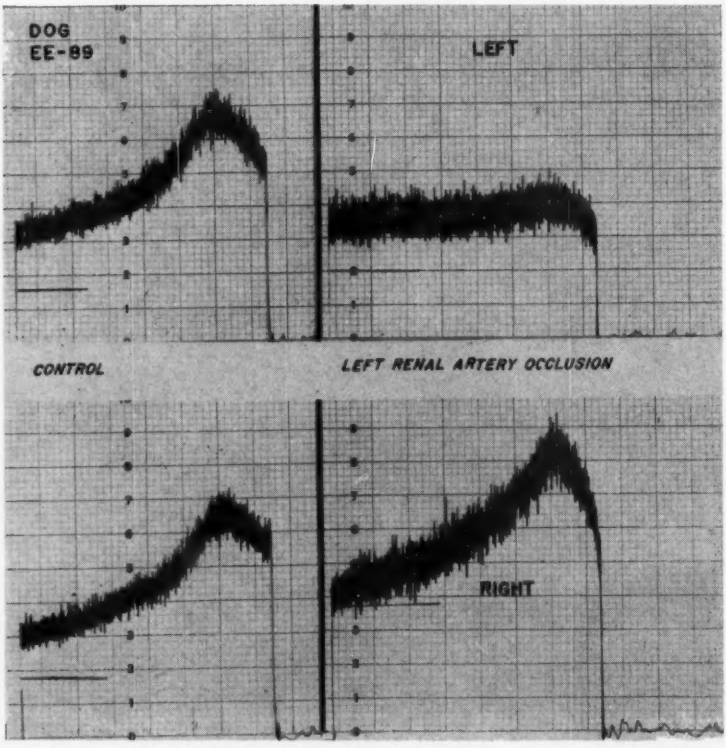

Fig. 2. Renograms before and after left renal artery occlusion in small animal. Note cross-monitoring of right (un-ligated) kidney by probe over left (ligated) kidney.

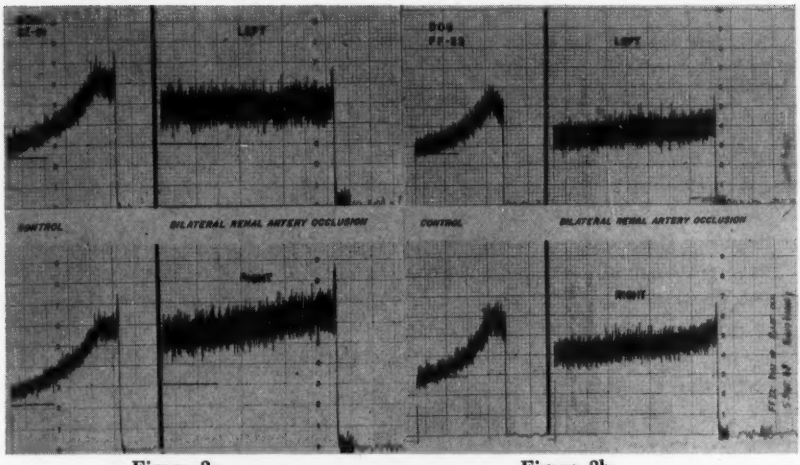

Figure 3a Figure 3b

Fig. 3a. Renograms before and after bilateral renal artery occlusion demonstrating no concentration of radioisotope by either kidney following ligation. Tracing similar to blood curve.

Fig. 3b. Same as 3a.

in the renogram pattern was noted. In two animals distinctively abnormal, but not diagnostic, renograms were obtained. Renal function determinations in these two animals revealed only mild diminution of renal function.

Renal function measurements in the remaining 7 animals demonstrated almost total renal shutdown. Examination of these kidneys after sacrifice of the animals revealed them to be pale and swollen. Microscopically, there was tubular

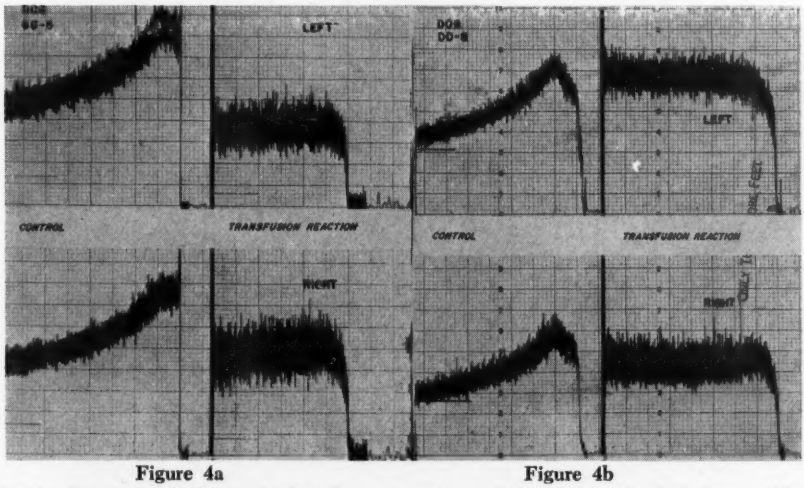

Figure 4a Figure 4b

Fig. 4a. Renograms before and after sham operation and transfusion of whole human blood in sensitized animal. Note early concentration of radiosotope by kidneys without demonstrable excretion.

Fig. 4b. Same as 4a.

swelling and necrosis with hemoglobin and cellular casts. Figures 4a and 4b demonstrate the characteristic type of renogram seen in each of these animals. Following an arterial spike there was a rise in the renogram curve as the radioisotope was concentrated in the kidneys. This phase of concentration seen following transfusion reaction was not seen in those animals in which renal artery ligation was performed, and is the differentiating characteristic of these curves. After the phase of concentration the curves became flat and there was no evidence of excretion of the radioisotope.

Figure 5 demonstrates the typical renogram curve seen following bilateral ureteral ligation in all four animals in Group 3 in which this procedure was performed. These renogram curves continued to rise throughout the tracing as the radiosiotope was concentrated by the kidneys and excreted into the renal pelvis from which it could not escape. These curves are similar to and confirm previous reports of the renogram pattern seen following bilateral ureteral obstruction. (9, 10, 13)

Figure 6 shows the renogram obtained in the patient with "lower nephron nephrosis". The curve was similar to that seen in the animals of Group 2 and demonstrated concentration of the radioisotope by the kidneys without evidence of excretion. On the basis of this tracing it was concluded that anuria was not on a mechanical basis, and this was confirmed at autopsy.

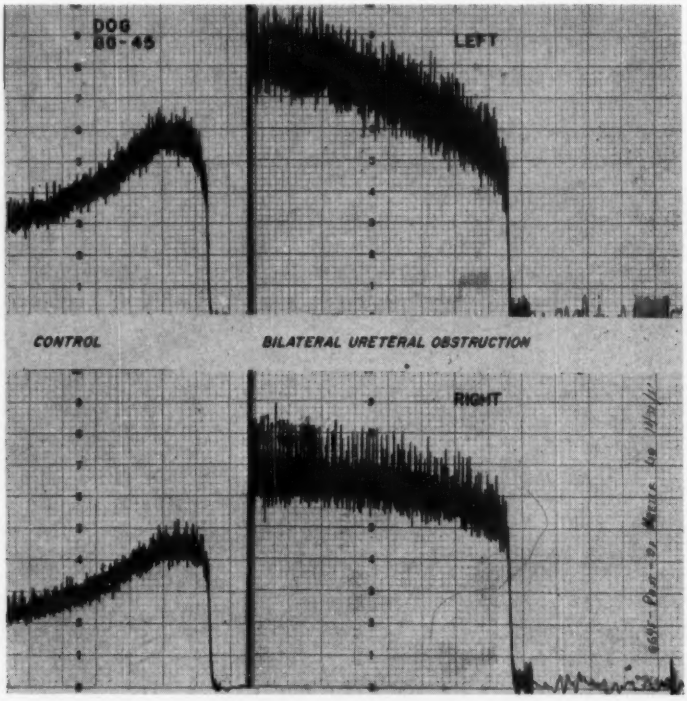

Fig. 5. Renograms before and after bilateral ureteral obstruction demonstrating continued concentration of radioisotope in region of kidneys throughout tracing.

DISCUSSION

Surgical relief of acute anuria of renal circulatory origin or due to bilateral ureteral obstruction is available, if a rapid and accurate method of diagnosis is possible. (14) As previously noted, the circulatory status of the kidneys may be determined by aortography, but this imposes certain difficulties and hazards in

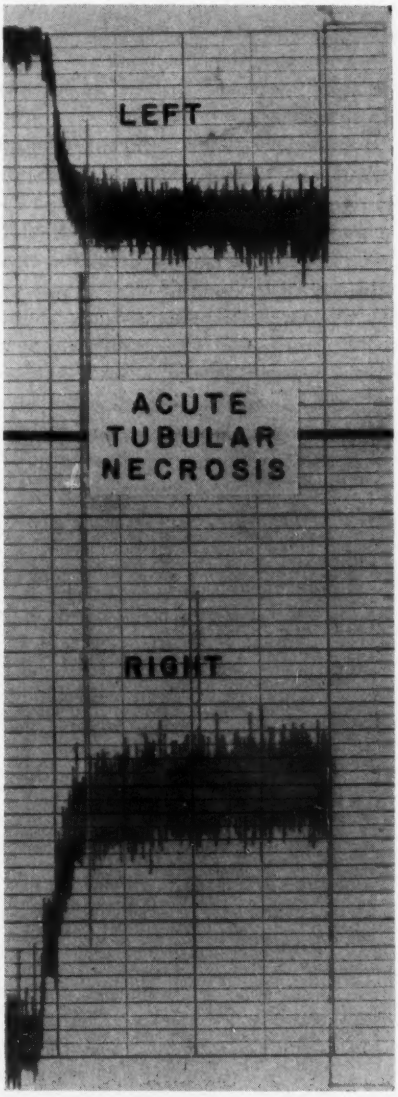

Fig. 6. Renogram in human with "lower nephron nephrosis". Note similarity to Fig. 4a and 4b.

the immediate period following operation. Ureteral patency may be determined by ureteral catheterization, but this also imposes additional problems and dangers in the patient with acute anuria. The results of this investigation would appear to indicate that the radioisotope renogram can be used to differentiate the various causes of renal insufficiency following vascular surgical procedures on the aorta and renal arteries.

Our renographic equipment is portable and can be taken to the patient's bedside (Fig. 7). The renograms can be made in the supine position, without turning the patient. A test dose and the tracer dose of the isotope can be injected through the intravenous tubing normally present in the period following operation, and no hazards to the patient are involved. The tracing requires only 20 minutes. Excluding those animals in which technical difficulties were encountered, those studied prior to standardization of technics and those dying before a study was completed, typical renogram patterns were seen in each group as demonstrated in Figure 8. The normal or control tracings demonstrated an arterial spike followed by a phase of concentration and a phase of excretion. If the arterial supply of the kidneys was not intact, the isotope was not concentrated in the kidneys and a blood curve resulted. Following a transfusion reaction the kidneys concentrated the isotope, but no phase of excretion was seen. If the ureters were blocked, the phase of excretion was lost and there was a sustained rise in the renogram curve throughout the period of the tracing.

In the single clinical instance in which the radioisotope renogram was used to determine the cause of renal insufficiency following abdominal aortic vascular

Fig. 7. Portable renogram equipment with which tracing obtained at bedside.

surgery, a curve typical of that seen with a transfusion reaction was noted. At autopsy ureteral patency and an intact renal arterial circulation were demonstrated. Efforts now are being made to obtain radioisotope renograms on all patients with renal insufficiency in a further effort to confirm these experimental findings. Although the instance of renal insufficiency following aortic surgery has been reported to be quite high in some centers, it has occurred only rarely in the Baylor University College of Medicine Affiliated Hospitals. Therefore, the majority of patients with renal insufficiency available for study have been those with medical uremia.

SUMMARY

Otherwise successful operations on the aorta and renal arteries are occasionally complicated by acute renal insufficiency, due to transfusion reactions or occlusion of the renal arteries. A rapid and accurate method of determining the cause of renal insufficiency in these patients is necessary if they are to be managed successfully. To determine if the I_{131} orthoiodohippuric acid renogram could be used in the differential diagnosis of renal insufficiency following aortic and renal artery surgery, these clinical conditions and bilateral ureteral obstruction were experimentally simulated in dogs.

In each group of animals distinct renogram curves were seen. In contrast to the normal renogram in which an arterial spike is seen, followed by a phase of concentration and a phase of excretion, no phase of concentration was seen in

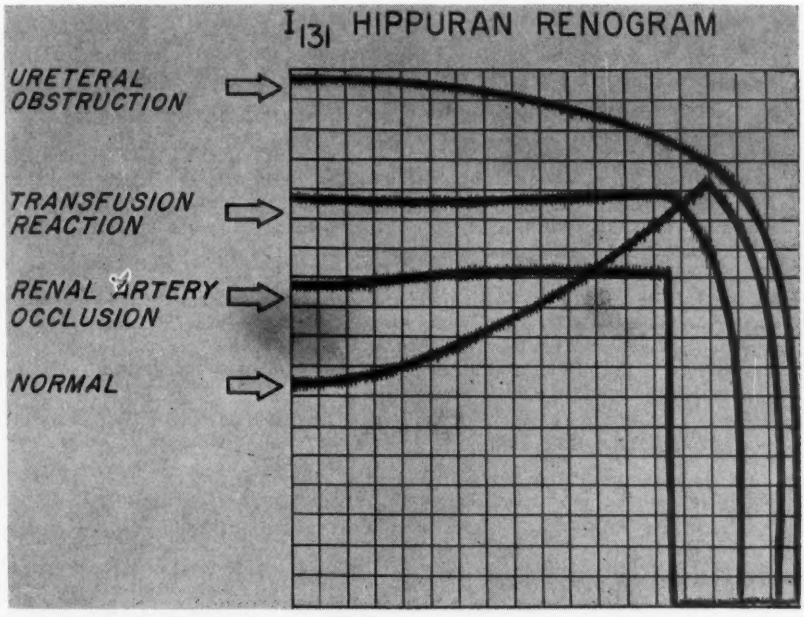

Fig. 8. Composite drawing of normal renogram and renograms following bilateral renal artery occlusion, transfusion reaction and bilateral ureteral obstruction.

those animals in which the renal arteries were ligated. Following a transfusion reaction an arterial spike and a phase of concentration were seen; however, there was no phase of excretion. If bilateral ureteral obstruction was produced a rising concentration of the radioisotope was seen throughout the renogram tracing. The radioisotope renogram has been useful in determining the cause of acute renal insufficiency in one clinical instance and further clinical studies are in progress.

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Evaluation of Quantitative Aspects of the Radioisotope Renogram[1]

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INTRODUCTION

A considerable amount of information has been published on the radioactive renogram since it was developed and first reported by Taplin (1) and Winter (2) in 1956. They suggested that this test would aid in the diagnosis of unilateral renal disease, and Winter later recommended it in particular as a screening test for unilateral renal disease as a possible cause of surgically reversible hypertension (3). The test was believed to be only qualitative, primarily because of the many variables inherent in this technique. Nevertheless, attempts have been made to increase the clinical value of the test by developing the technique in such a way that the test could also render quantitative information (4).

The present report describes the empirical development of a technique intended to control as many variables as possible, sets forth certain parameters for which ranges of normal values could be established, and compares the results obtained in normal and diseased kidneys with this technique and the selected parameters.

The variables we attempted to control in the first step of our study were the following:

1. Instrumental variation. Its principal source lies in fluctuations in the power supply and in differences in sensitivity of the detector probes (originating mostly in the photomultiplier tubes). These difficulties were met by the use of a "precision power supply" equipped with a stabilizer and a solar transformer and a linear amplifier-discriminator combination respectively. In addition, of course, an adequate method of calibration (see below) was used.

2. Variation in kidney-detector geometry. We elected to carry out the renogram tests with the patients horizontal, in the supine position, and the

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detector probes vertical, pointing upwards, each covering with its collimator opening the lower half of a kidney. The location of the kidney was marked on the patient's back with the help of supine "IVP" or "KUB" films. This arrangement appeared to offer the highest degree of reproducibility of kidney-detector geometry as the force of gravity would presumably tend to place the kidney always in the same spot regardless of variations in the elasticity of the supporting pararenal tissue (Fig. 1).

3. Differences in state of hydration. This variable has a very pronounced effect upon the renogram curve and it was therefore necessary to standardize the state of hydration. We chose dehydration for a period of 12 hours, as we had found previously that differences in function between the left and the right kidney sometimes did not appear in hydrated patients, while appearing distinctly after dehydration (Fig. 2).

4. Differences in blood volume. As the blood concentration of labeled compound passing through the kidneys determines the count rate, and as this concentration is determined by the strength of the dose and the size of the blood volume, we feared that the expected variations in blood volume may significantly influence the count rate and thus the recording when using constant

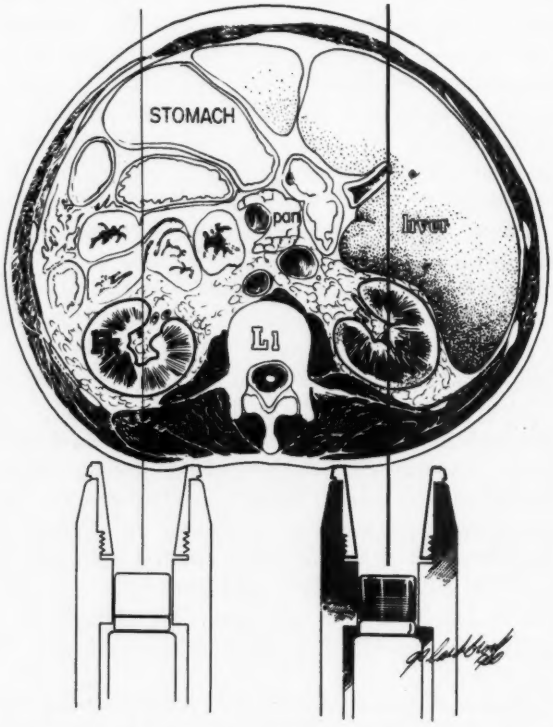

Fig. 1. Body cross-section showing the geometrical relation between detectors and kidneys of the supine patient.

doses. To minimize the effect of this variable, we based the strength of the dose on the estimated blood volume.

In the choice of our technique we received considerable help from information obtained by a previous group of investigators of this institution (5).

MATERIALS AND METHODS

1. *Test Subjects.* Two groups were selected. The first consisted of nine normotensive males, ranging in age from 24 to 52 years, who had normal blood urea nitrogen, no clinical evidence of renal disease, no abnormality of urinalysis, and no abnormality detectable by whatever X-ray examination they had, "KUB" or "IVP" films. Each had 2 renograms, with a minimal interval of 24 and a maximal of 48 hours. The second group of patients consisted of 14 hypertensive patients of both sexes who subsequently came to operation. In addition to one

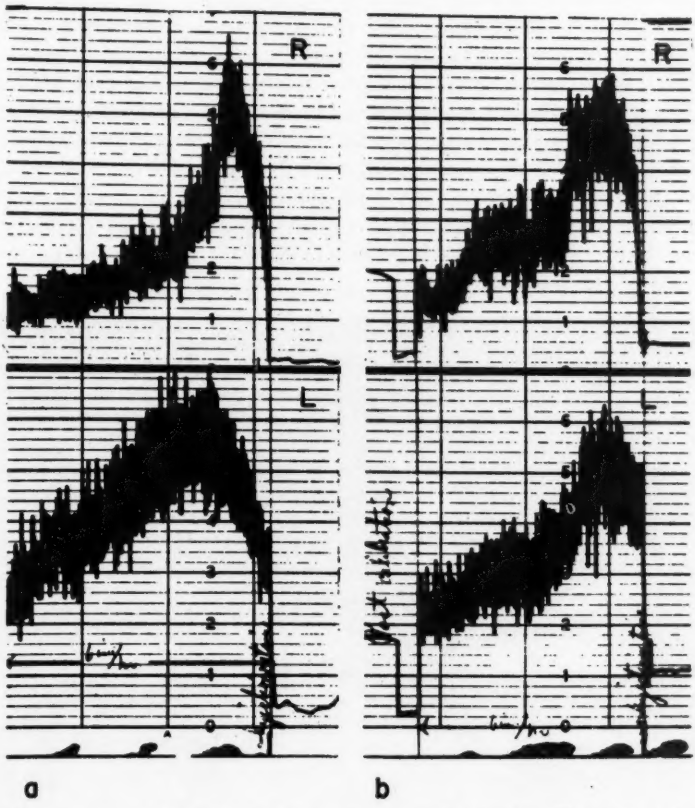

Fig. 2. Two renograms of a patient who had had a renal calculus on the left: (a) in dehydrated state; (b) in state of hydration. Note that a diagnostic difference between the right and left kidney curve appears in the state of dehydration, but not in the hydrated state.

renogram, each patient in this second group had several other renal studies, most often arteriograms and differential renal function (Howard) tests.

2. *Instrumentation.* An arrangement of the following components was used (Fig. 3): 2 scintillation detectors, each equipped with 1.5″ × 1″ sodium iodide crystal and a 36 degree flat field collimation; 2 rate meters, each equipped with a linear amplifier-discriminator combination; 1 dual rectilinear recorder equipped with a time marker pen.

The instrument settings were as follows: Time constant, 0.5 seconds; rate meter scale, 10,000 counts per minute; recorder speed, 6″ per hour or 6″ per minute. The detectors were directed vertically upwards and each of them centered over one kidney.

The method of calibration was as follows: The right rate meter was calibrated daily using a mock iodine source. The left rate meter was then tested against the right for uniform response, using two volumetric flasks each containing 0.5 microcurie of I-131 and carrier in 250 ml of water. These volumetric flasks were placed in the collimator opening of the upward directed probes, which provided constant and reproducible geometry.

3. *Test Materials.* As previous experience had suggested that I-131 labeled iodohippuric acid (Hippuran) is superior to other labeled compounds in renography (6), we used this compound. The dose was 15 microcuries per square meter of surface area, determined from the height and weight of the patient with the DuBois normogram, also used for estimation of blood volume. The volume of the injected dose was kept constant by withdrawing blood up to the 1 ml mark before injection. The beginning of injection was marked on the record with an electric time marker pen.

Fig. 3. Instrument arrangement for performing renograms. See text for components.

4. *Technique.* Subjects drank no fluid after 10:00 P.M. the night before the test. The outline of the kidney was marked on the patient's back, using tracings from "IVP" or "KUB" X-ray films, and using the iliac crest, twelfth rib and spinal processes as landmarks. The test subjects were placed supine on the table, which had a tranverse slit of adjustable width at the level of the kidneys. The detector probes were placed through this slit perpendicular to the patient's back and directed upwards (Fig. 1).

5. *Method of Measurements.* Twenty-eight parameters (Table I) were determined for each of the nine normal patients. As each of these normal subjects had bilateral renograms performed twice, the parameters 1 through 14 were each determined on a total of 36 tracings, and the parameters 15 through 28 were each determined on a total of 18 pairs of tracings. Figure 4 shows a typical renogram curve, with the points and lines of measurement superimposed upon it.

Parameters 12, 13, 14, and 26, 27, 28, are angles expressed in degrees; all others, including those referring to time (parameters 4, 5, 10, 11, 18, 19, 24, and 25), were actually determined by linear measurement on the recorder paper and are expressed here in millimeters.

Two different recorder speeds were used, 6 inches per hour and 6 inches per minute. Most of the recordings were made at a paper speed of 6 inches per hour, as this speed proved most convenient. However, parts of some recordings were

TABLE I

PARAMETERS OF THE RENOGRAM

1.	bB*	:	the maximum of counts per minute (Abbr.: maximum count)
2.	cC	:	the count per minute at 15 minutes after injection (Abbr.: count at 15 minutes)
3.	B-C	:	the difference between maximum count and count at 15 minutes
4.	ob	:	the time after injection at which the maximum count occurs (Abbr.: time of maximum count)
5.	bc	:	15 minutes minus time of maximum count
6.	$\frac{100}{ab}$	:	the slope of renal uptake extrapolated to zero count (expressed in percent of Bb per minute)
7.	$\frac{B}{ob}$	:	rate of total uptake
8.	$\frac{B\text{-}C}{bc}$	:	rate of excretion from the time of maximum count to 15 minutes after injection
9.	$\frac{B}{C}$	:	ratio of maximum count to count at 15 minutes
10.	00_1	:	half-time uptake (not marked on figure)
11.	bd	:	half-time excretion
12.	α	:	angle of extrapolated uptake slope
13.	β	:	angle of rate of total uptake slope
14.	γ	:	angle of rate of excretion slope
15.	$-28.$	:	differences of the parameters 1-14 between the left and right kidney

*For significance of the geometrical notations, see Figure 4.

made at a speed of 6 inches per minute, when detailed information about certain phases of the test (especially initial events after injection) was desired. Whenever such a change in recorder speed was made, all measurements were corrected back to a speed of 6 inches per hour, *i.e.*, the expansion was reduced to the scale of 1 minute per 1/10 inch of recording paper. Therefore, all time values can be converted from millimeters to minutes, if desired, by dividing by the factor 2.54.

6. *Method of Analysis for Obtaining Normal Ranges.*

Establishment of useful "tolerance" ranges from the responses of the normotensive subjects required: 1) that such responses indicate a normal distribution among normotensive individuals and 2) a method which would take into account that a normotensive subject had two renograms while a hypertensive patient had only one.

The normality of the observations on the normal persons was evaluated by use of probability paper. The plotting position of each value was determined by the equation $p_i = (i - \frac{3}{8})\ (n + \frac{1}{4})$ where i represents the numerical rank of a given value among n observations (7).

For each of the parameters numbered 1 through 14 (Table I), the values for both observations of the right kidney in all nine patients were plotted as one set. Those for the left kidney were similarly plotted. For each parameter numbered

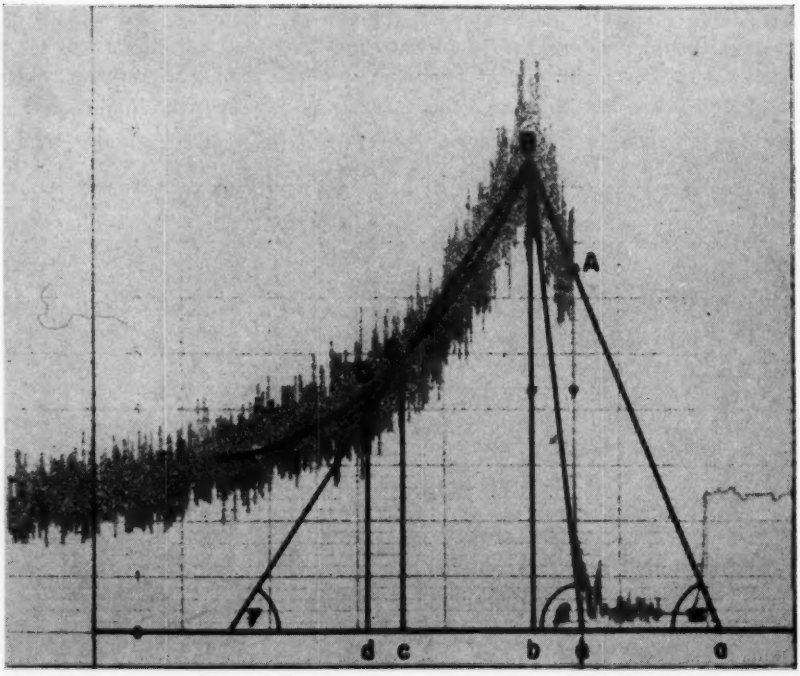

Fig. 4. Normal renogram, with geometrical and analytical data superimposed. For method of measurements, see text. The record is made from right to left.

15 through 28, the differences between simultaneous renograms of the left and right kidneys were plotted with the algebraic sign preserved. An additional set of plots were obtained with the algebraic sign ignored. In every instance, 18 individual values were included in the plot.

When the observations for a given parameter did not appear to be normally distributed, no further analysis was attempted. Those which appeared to have a normal distribution were analyzed in the following manner: First, the following relationship was assumed.

$$x_{ij} = \mu + t_i + e_{ij}$$

where

x_{ij} = the single observation
μ = the mean response of normotensive persons
t_i = the deviation of the i_{th} individual's mean response from μ.
e_{ij} = the deviation of the j_{th} observation on the i_{th} individual from the individual's mean response

It follows then that the variance of the single observations represents the sum of the variance associated with variation among patients and the variance associated with variation within patients, or

$$\sigma_x^2 = \sigma_t^2 + \sigma_e^2$$

Then, with

1) n = number of observations on each individual
2) k = number of individuals
3) $\bar{x}_i$ = mean of the n observations on the i_{th} individual
4) $\bar{x}$ = mean of the kn observations

5) $\dfrac{n \Sigma (\bar{x}_i - \bar{x})^2}{k - 1} = MS_A$, an estimate of $\sigma_e^2 + n\sigma_t^2$

6) $\dfrac{\Sigma (x_{ij} - \bar{x}_i)^2}{K(n - 1)} = MS_W$, an estimate of σ_e^2

we have an estimate of the variance of single observations, namely:

$$s_x^2 = \frac{n - 1}{n} MS_W + \frac{1}{n} MS_A$$

The number of degrees of freedom associated with s_x^2 was obtained after Satterthwaite (8) and computed as follows:

$$f = \frac{\left[\dfrac{n - 1}{n} MS_W + \dfrac{1}{n} SM_A\right]^2}{\dfrac{\left[\dfrac{n - 1}{n} MS_W\right]^2}{k(n - 1)} + \dfrac{\left[\dfrac{1}{n} MS_A\right]^2}{k - 1}}.$$

The value of s_x and its accompanying degrees of freedom were then used to obtain three tolerance ranges with confidence coefficients equal to 95 per cent.

The first tolerance range represented the limits within which at least 75 per cent of single observations on normotensive persons would be expected to fall. At least 90 per cent would be expected to lie within the second range; at least 95 per cent, in the third. Limits of the ranges were computed by

$$\bar{x} \pm ks_x$$

where k was determined by the confidence coefficient (95 per cent), the proportion to be included (75, 90, or 95 percent), and the number of degrees of freedom. (9).

RESULTS

1. As one of the purposes of this study was to find the parameters of the renogram curve that are best adapted to systematic analysis, we discarded parameters for which the observations did not have normal distribution, as explained under "Method of Analysis for Obtaining Normal Ranges." Table II shows all estimates associated with those parameters that had observations with apparently normal distribution. As the data in the left half of Table II indicate, normal distribution of the observations for *both* kidneys was not found in the case of any of the angles; it should be noted that the angles measured here all had limits of 90°. Differences between kidneys showed very high standard deviations in proportion to the means. Furthermore, differences between kidneys would not in any event lend themselves well to the type of analysis given in Table IV, where all observations were related to single kidneys, not patients. Observations of differences between right and left kidney would not be referrable to a single kidney, when both kidneys in the same patient were abnormal. Therefore, the remaining parameters, *i.e.*, the first three listed in Table II, appeared to be most suitable for systematic analysis.

2. Figure 5 and the right half of Table II indicates the ranges within which 75 per cent, 90 per cent, and 95 per cent of normal individuals would be expected to fall.

3. As most of the 14 abnormal patients studied had unilateral renal disease, they provide an opportunity for comparison of normal and abnormal kidneys in the same patient. This comparison is presented in Tables III and IV, Table III presenting the results for the three most suitable parameters in the 14 abnormal patients studied and Table IV presenting a summary of the data in Table III, showing the number outside the normal range. From this summary, it is obvious that the time of maximum count appears to be the most useful parameter. Among the 13 normal kidneys, all observations fell within the 75 per cent range. Among the 15 abnormal kidneys, 8 observations fell out of the 75 per cent range, 7 out of the 90 per cent range and 7 out of the 95 per cent range. The differences between normals and abnormals are significant for the 75 per cent range ($P<0.005$) and 90 per cent and 95 per cent ranges, ($P<0.01$).

None of the four left renal lesions was associated with a prolonged time of maximum count (using the 95 per cent normal range). All abnormal kidneys associated with such a prolongation were on the right.

The values for maximum count and count at 15 minutes showed no significant differences between normal and diseased kidneys. But in every patient with

TABLE II

RANGE OF EXPECTED NORMAL RENOGRAM VALUES AS DERIVED FROM DUPLICATE STUDIES OF 9 NORMAL INDIVIDUALS

Parameter		*Mean*	*Sx***	$\frac{Sx}{Mean}$	*Proportion Included in Range** 75%	90%	95%
Maximum Count	R	58.81	15.83	.2692	30.16 – 87.46	17.86 – 99.76	10.04 – 107.58
Bb	L	81.44	21.43	.2631	40.38 – 122.50	22.79 – 140.09	11.60 – 151.28
Count at 15 min.	R	27.44	13.10	.4774	3.10 – 51.78	0 – 62.22	0 – 68.86
Cc	L	38.81	12.69	.3270	17.17 – 60.45	7.88 – 69.74	1.97 – 75.65
Time of Max. Ct.	R	12.14	3.56	.2932	6.16 – 18.12	3.60 – 20.68	1.97 – 22.31
ob	L	14.33	4.22	.2945	6.84 – 21.82	3.63 – 25.03	1.59 – 27.07
Angle α	R	62.69	12.57	.2005	40.88 – 84.50	31.52 – 90.00	25.56 – 90.00
Angle γ	R	48.89	13.70	.2802	22.64 – 75.14	11.39 – 86.39	4.24 – 90.00
Diff. Cc (Absolute)***	L-R	13.69	8.22	.6004	0 – 28.57	0 – 34.96	0 – 39.02
Diff. $\frac{100}{ba}$ (With Sign)***	L-R	.1894	.9654	****	(−1.408) – (+1.787)	(−2.095) – (+2.474)	(−2.532) – (+2.911)
Diff. $\frac{B\text{-}C}{bc}$ (Absolute)***	L-R	.8828	.4660	.5279	.100 – 1.665	0 – 2.001	0 – 2.215

* each range has an accompanying 95% confidence coefficient.
** standard deviation
*** differences between left and right kidney in the parameters 6-8, respectively, of Table I
**** not computed since all values were not positive
All values are expressed in millimeters.

TABLE III

RESULTS OF RENOGRAMS IN 14 INDIVIDUALS WITH RENAL OR PERIRENAL DISEASE

Patient	*Final Diagnosis†*	*Abnormal Kidney(s)*	*Normal Kidney(s)*	*Maximum Count*		*Renogram Values†† Count at 15'*		*Time of Max. Ct.*	
				Right	*Left*	*Right*	*Left*	*Right*	*Left*
B. B.	Stenosis of left renal artery	Left	Right	72	63	25	31	9½	10
G. L.	Stenosis of both renal arteries; more marked on the left	Both	None	90*	67	67**	42	24***	15
P. A.	Stenosis of right renal artery	Right	Left	56	67	44	28	30***	13
S. L.	Infarct of lower half of left kidney	Left	Right	102**	48	52*	38	17	18
P. R.	Cyst of right kidney with vascular obstruction	Right	Left	50	52	35	39	9	10
H. L.	Stenosis of right renal artery	Right	Left	101**	112	97***	77***	33***	13
M. O.	Stenosis of right renal artery	Right	Left	72	118	66**	46	51***	18
F. J.	Thrombosis of aberrant artery to lower pole of right kidney	Right	Left	40	58	35	38	24***	17
Mc S.	Stenosis of both renal arteries; more marked on left	Both	None	57	37**	42	21	20	12
C. C.	Stenosis of right renal artery	Right	Left	65	111	64**	56	34***	11
O. J.	Infarction of mid-section of right kidney	Right	Left	24*	54	16	40	16	16
C. A.	Pyelonephritis c contraction of right kidney	Right	Left	81	112	75***	49	29½***	11
H. B.	Pyelonephritis with contraction of left kidney	Left	Right	90*	58	68**	54	18	15
P. J.	Adenoma of left adrenal	None	Both	75	104	51	68*	17	16

*values outside the 75% range **values outside the 90% range ***values outside the 95% range
†All diagnoses were established at surgical operations. ††All values are expressed in millimeters.

unilateral renal disease, the maximum count was higher on the normal than on the abnormal side.

In addition to showing the number of times a given observation fell outside the normal range in the 14 abnormal patients studied, Table IV also separates observations falling outside the normal range into those which fell *above* the range and those which fell *below* it. When the maximum count fell outside the normal range, it sometimes fell above this range and sometimes below it. The time of maximum count and the count at 15 minutes, however, never fell below the normal range in the 14 patients summarized in Table IV; observations for these two parameters always fell either in the normal range or above it.

DISCUSSION

The *most suitable parameters for analysis* must almost certainly be among those listed in Table I, as we began our study by including virtually every parameter of the renogram curve that was subject to linear or angular measurement. The criteria for elimination of many of these parameters in the final analysis

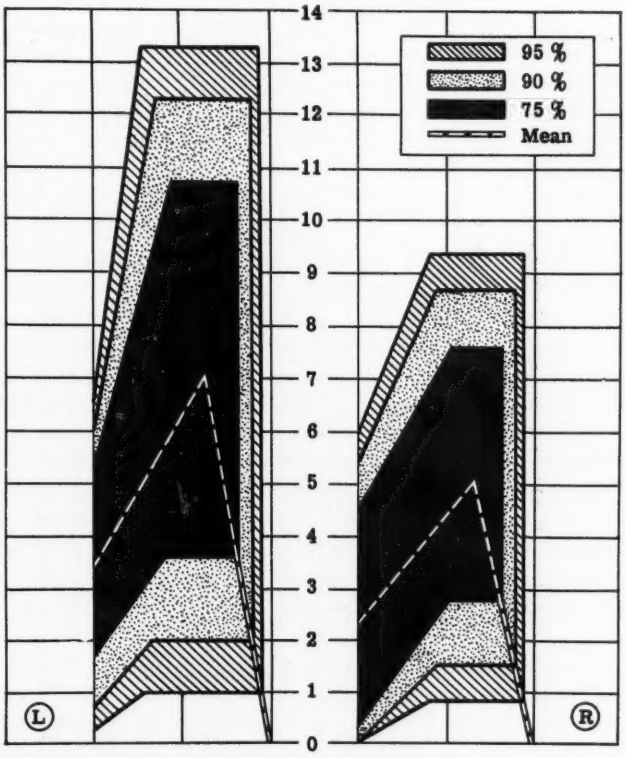

Fig. 5. Schematic renogram, derived from statistical analysis of nine normals. The dotted line represents the mean of maximum count, of time at maximum count, and of count at 15 minutes. The shaded areas represent: the ranges within which 75, 90, and 95 per cent of normals would be expected to fall.

TABLE IV

PROPORTION OF ABNORMAL RENOGRAM RESULTS IN THE 14 INDIVIDUALS LISTED IN TABLE II

	Diseased Kidneys				*Normal Kidneys*			
	Total Number	*Number Falling Outside Expected**			*Total Number*	*Number Falling Outside Expected**		
		75% Range	*90% Range*	*95% Range*		*75% Range*	*90% Range*	*95% Range*
PATIENTS WITH VASCULAR LESIONS								
Maximum Count	13	4 (±±)	1 (+)	0	9	1 (+)	1 (+)	0
Count at 15′	13	4 (+)	4 (+)	1 (+)	9	2 (+)	1 (+)	1 (+)
Time of Max. Ct.	13	7 (+)	6 (+)	6 (+)	9	0	0	0
PATIENTS WITHOUT VASCULAR LESIONS								
Maximum Count	2	0	0	0	4	1 (+)	0	0
Count at 15′	2	1 (+)	1 (+)	1 (+)	4	2 (+)	1 (+)	0
Time of Max. Ct.	2	1 (+)	1 (+)	1 (+)	4	0	0	0

*(+) and (−) indicate results falling above or below the normal range, respectively.

have been mentioned under "Methods of Analysis for Obtaining Normal Ranges" and "Results". We preferred this method to one involving *a priori* assumptions regarding the physiologic significance of the various portions of the renogram curve. If the precise physiologic significance of each detail of the curve were thoroughly understood, one might more logically select parameters on the basis of their established physiologic importance. In the absence of such knowledge, however, the method used here seemed preferable.

Establishment of *the range of normal values* was a major aim of this study and as the term "normal range" is vague when given without mention of the confidence level and the percentage of normal individuals expected to fall within this range, we have sought this information also. Knowledge of the normal range is indispensable to the interpretation of any test. Thus, even if one should subscribe to the view that the renogram is to be considered merely a qualitative test seeking to establish, whether there is a difference between the two kidneys of any individual, knowledge of the normal range of the difference would still be necessary. Furthermore, knowledge of the normal range is particularly important in making a preoperative decision as to which side is abnormal, once a difference between the two kidneys has been noted. It should be noted that, even in normal individuals, the two kidneys seldom give precisely identical curves. The difference in normal ranges for left and right side, as established by the present study, is consistent with other studies of renal function in normal individuals (10). However, it must also be admitted that our method of calibration may not have succeeded completely in matching the two detector probes and, in spite of careful calibration, some of the difference between left and right kidney may still represent instrumental artifact.

In view of the increased width of the normal range for the renogram on the left, it is not surprising that we were more successful in correctly diagnosing right renal lesions than those on the left.

It appeared to be important that the test be as quantitative as possible, and that the normal range of the various parameters of the renogram curve be carefully established because of the following consideration. Renography, renal scanning, pyelography and arteriography (with its associated nephrography and nephrotomography) are the tests which offer the possibility of giving information about the function of one kidney as compared to the other, without insertion of ureteral catheters. However, arteriography and pyleography are, for inherent reasons, unable to give quantitative information, despite their undoubted value in other respects. Therefore, the renogram and the renoscan remain the techniques offering the possibility of yielding quantitative information about differential renal function in the absence of ureter catheterization.

The width of the normal range, even with the improvements in technique listed here, remains somewhat discouraging. Furthermore, our analysis suggests that in general day-to-day variations in a single patient's renogram are appreciable, though less than the variations from patient to patient. Normal physiologic variations in the state of renal function and individual differences in thickness of the absorbing tissue between the kidney and the detector were not controlled by our present technique and, indeed, will probably continue to be difficult, if not

impossible to control. Therefore, it will probably be necessary to pay still further attention to controlling those variables that are at least theoretically within reach of experimental control. Among these, the most critical one is probably the kidney-detector geometry.

In *the correlation of results with clinical findings*, the demonstration of the importance of the time of maximum count as an indication of vascular lesions seems thoroughly reasonable. It should be stressed that we now make this statement on the basis of precise measurements in patients with proved lesions, after comparison with an established normal range, rather than on the basis of an *a priori* assumption.

The failure of other parameters to provide diagnostic information is disappointing and is most probably due to the width of the normal range. If, as discussed above, further attention to control of variables in the technique decreases the width of the normal range, it is quite possible that additional parameters will begin to show diagnostic significance. We again stress that such diagnostic significance can only be accepted if demonstrated by comparison of normal individuals with patients having pathologically proven renal disease.

Although the maximum count did not correctly indicate abnormality in any patient, as judged by our present criteria, it should be noted that this parameter did show a tendency to be elevated in the *normal* kidney of every patient with unilateral renal disease. This suggests the possibility of a compensatory mechanism and may eventually become useful as at least a minor diagnostic clue.

SUMMARY

Renograms were performed twice, under carefully standardized conditions, on each of nine normotensive individuals who had, by clinical criteria and conventional laboratory tests, no evidence of renal disease. Twenty-eight parameters of each of these normal renograms were measured and normal ranges established for the three parameters which appeared most suitable on the basis of statistical analysis. These three parameters were the maximum count, the count at 15 minutes after injection and the time of maximum count.

Renograms were performed on fourteen individuals with suspected renal disease, in whom the diagnosis was subsequently established at operation, and the diagnostic usefulness of the three chosen parameters was evaluated by comparison of the renogram from abnormal kidneys with the normal standards. The time elapsing between injection of the labeled material and the attainment of maximum uptake over the kidneys (time of maximum count) proved the most reliable criterion of renal vascular disease. Among 13 kidneys with vascular disease, 7 showed times of maximum count falling outside the 75 per cent normal range, and 6 showed times of maximum count falling outside the 95 per cent normal range.

Although the renogram thus has diagnostic usefulness when studied in a quantitative manner, the normal range is sufficiently wide to interfere with the use of the renogram, in its present form, as a reliable screening test for unilateral

renal disease. However, there is some basis for the hope that further improvement of the technique may decrease the width of the normal range and presumably increase the diagnostic value of the renogram.

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Liver Function Related to Thyroxine Metabolism[1,2]

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Recent studies regarding thyroxine metabolism have exposed several unexpected problems. Part of the hormone is deiodinated in the body but it is not clear if this process simply destroys the hormone or whether it intensifies its action by production of triiodothyronine (1, 2). The deiodination is inhibited by several thiouracil type compounds in the rat and by propylthioracil in the human being (1, 3). Yet, biological importance of this inhibited deiodination is unknown (3, 4).

The human liver has been observed to concentrate injected radiothyroxine (8), however the importance of this concentration is not clear and the degree of concentration has not been satisfactorily measured. Thyroxine is excreted by the liver in the bile as a poorly absorbable glucuronide conjugate (9, 10). In the lower intestine the glucuronide is hydrolyzed, producing thyroxine that is found in the feces. Part of the thyroxine is believed to be reabsorbed and carried directly to the liver, thereby completing an enterohepatic circulation of the thyroid hormone.

Lennon *et al.* (6) showed that patients with liver disease had severely impaired removal of thyroxine from the plasma. Their results are related to those of Vannotti *et al.* (7) which proved thyroxine glucuronide to be absent in bile of patients with hepatitis.

Thyroxine therapy is always given by the oral route but recent studies (5) have shown that there are differences in the metabolism of oral thyroxine compared to the intravenous administration. After oral thyroxine approximately 35-40 per cent of an oral dose was rapidly excreted in the feces of normal human

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[2]This investigation was supported by Grants A-4689 from the National Institute of Arthritis and Metabolic Diseases, USPHS, and Grant AT-(40-1)-1643 from the U. S. Atomic Energy Commission.

beings (5) and this fraction was independent of the daily oral dose of exogenous thyroxine, over the physiological range of 1 μg of tracer thyroxine to 180 mg of Thyroid U.S.P. (equal to 200 μg of thyroxine). These results are quite different from those obtained by parenteral administration of thyroxine in physiological or pharmacological doses (12). Another unusual and important property of thyroxine is that after thyroxine is absorbed it becomes firmly attached to a plasma inter-alpha globulin, TBG (11). In effect, this becomes a natural radioactive plasma protein, different from RISA in that it is a globulin and it is physiological.

The present experiments were begun to study the metabolism of I-131 L-thyroxine in normal human beings. The early experiments showed that liver concentration of thyroxine was easily visualized, therefore a survey was undertaken to test the value of abnormal radiothyroxine metabolism as a measure of liver function.

METHODS

The I-131 L-thyroxine[1] had a specific activity of 10-30 μc/μg, dissolved in 50 per cent propylene glycol. Repeated paper chromatograms showed only radiothyroxine and radioiodide to be present. Oral doses of 40 to 60 μc were adminis-

[1]I-131 L-thyroxine was obtained from Abbott Laboratories, Oak Ridge, Tennessee.

TABLE I

LABORATORY FINDINGS IN PAT ENTS WHOSE SCANS ARE ILLUSTRATED

Control Patients—no clinical evidence of liver disease.

Patient	*Figure No.*	*PBI (μg%)*	*Thyroid (U.S.P.) Therapy (mg/day)*	*Clinical Diagnosis*
R. J.	3	8.0	540	no physical disease
G. H.	1, 2	7.8	none	gastric ulcer
F. N.	4	7.3	240	thyroidectomy (papillary carcinoma)

Patients with cirrhosis of liver.

Patient	*Figure No.*	*Type of Cirrhosis*	*PBI (μg%)*	*BSP**	*A/G***	*Ceph. Floc.*	*Total Plasma Bilirubin*	*Biopsy (confirming cirrhosis)*
J. T.	5, 6	Infectious hepatitis (chronic)	7	6	3.3/4.2	3+	2	+
C. G.	7	Post hepatetic		33	1.5/5.9		3.4	none
L. B.	8	Laennec's	9.7	35	3.1/2.1	4+	1.6	+
M. B.	9	Undetermined	10.0	8	2.4/2.9	neg.	0.1	+
L. Q. J.	10	Laennec's	9	27	2.2/2.5	3+	.5	+

*Percent retention after 45 minutes, more than 5% is considered abnormal.
**Albumin/globulin ratio (gm%).

tered in freshly prepared water solutions.[1] After 6 hours, 24 hours and 96 hours photoscans were prepared using a Picker Magnascanner and a 19-hole honeycomb collimator. The scan required 60 to 90 minutes with the following settings: Scan speed 30 to 40 cm/min, line space 0.4 to 0.5 cm, c/m range differential 50 per cent, background cut-off 50 per cent, photorecorder light collimator 3 mm diameter, density 50,[2] range 1K, time constant ¼, dot factor 4, background 50, window 310-410 MEV. The ultervoltage of the photorecorder was set at 900 volts with probe over the left thorax (background). The xiphoid, umbilicus and costal margins were marked on the teledeltos tracing before the patient was removed from the counter.

Five patients with various abnormalities, had no clinical evidence of liver disease and they are considered to be controls. One had a gastric ulcer and another had gastroenteritis; they received only 2 μg of L-thyroxine with the radioactive hormone. Two other controls were taking 180 mg of Thyroid U.S.P. medication daily and another, although euthyroid, had taken by self-medication, 540 mg of Thyroid U.S.P. each day for 3 months.

Five patients had clinical diagnoses of cirrhosis, 4 of these had hepatomegalia, in three the BSP excretion was severely impaired and in 4 there were liver biopsies to prove cirrhosis. The cephalin cholesterol flocculation of 3 patients were diagnostic of liver disease and all had a subnormal plasma albumin.

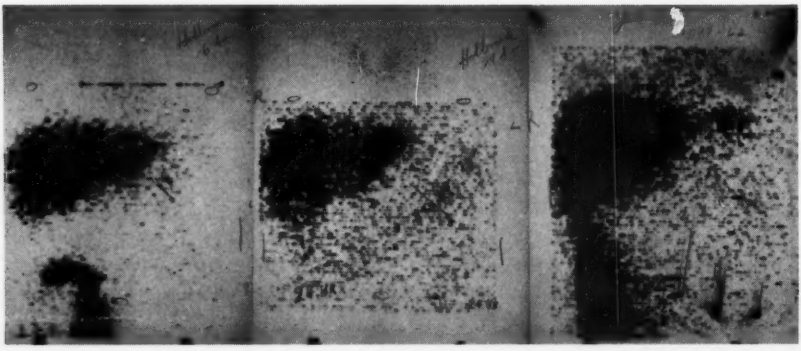

Figure 1 Figure 2 Figure 3

Control abdominal scans after oral I-131 thyroxine. Position of umbilicus and lower costal margin are shown as landmarks, occasionally the location of the nipples are shown.

Fig. 1. Was made 6 hours after 60 μc (2μg) I-131 L-thyroxine was orally administered to patient G. H.

Fig. 2. Shows that after 24 hours patient G. H. had excreted most of the intestinal radiothyroxine.

Fig. 3. Patient R. J. had been taking 540 mg of Thyroid U.S.P. daily for several months before 60 μc I-131 L-thyroxine was given. Scan shows liver and intestine 6 hours after injection of radiothyroxine.

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[1]For accurate measurement of administered dose, radioactivity of container must be measured before and after administration; the dose is the difference between the two measurements.

[2]With *Kodak Blue Brand Film* we used density setting of 50.

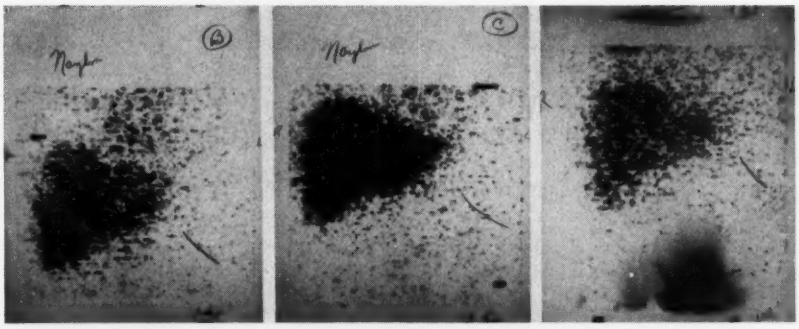

Fig. 4. Abdominal scan of patient F. N. after 40 μc I-131 L-thyroxine was given intravenously. The patient had been taking 180 mg. Thyroid U.S.P. daily for 6 months. One hour, 3 hours and 24 hours after radiothyroxine was given there was concentration of I-131 only in the liver. The black area in the lower part of the 24-hour picture is an artifact due to a light leak; it was absent from the teledeltos tracing.

RESULTS

Figure 1-3 show the sharp localization of radiothyroxine in the liver and in the intestine of normal patients. Figure 4 illustrates results in a control patient who was given intravenous I-131-thyroxine and scanned 1, 3 and 24 hours later; only the liver was intensely outlined on his body scan.

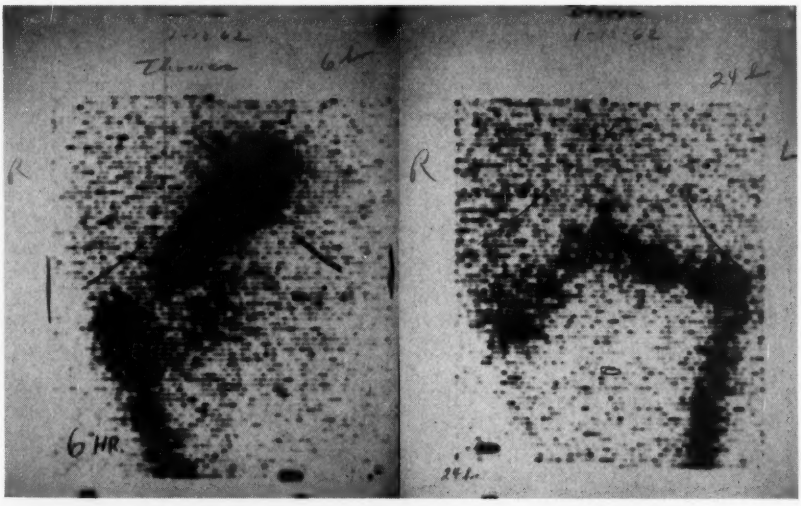

Figure 5 **Figure 6**

Patients with cirrhosis.

Five patients with liver cirrhosis were given 60 μc I-131 L-thyroxine orally. Minimal liver patterns appeared but intestinal patterns were very intense. Stomach is shown in Figure 5. Figure 5 refers to patient J. T., 6 hours after radiothyroxine and Figure 6 was made from the same patient 18 hours later.

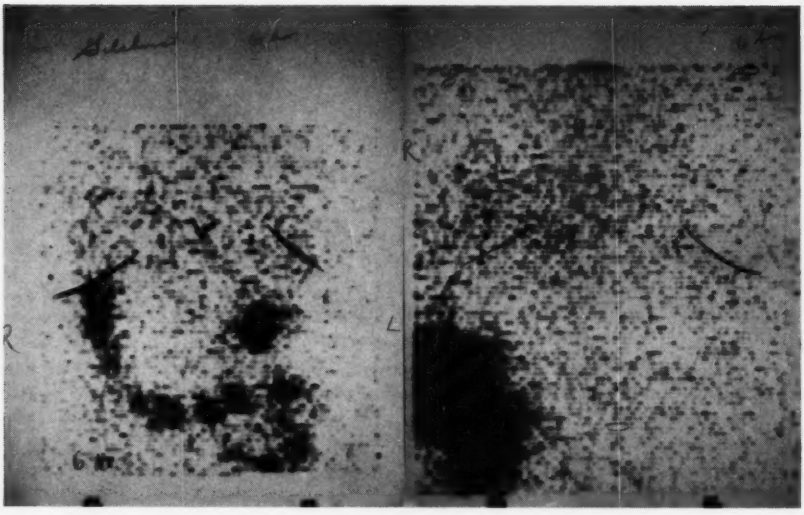

Figure 7 Figure 8

Fig. 7, 8 and 9 refer to patient C. G., L. B. and M. B., each 6 hours after the radiothyroxine.

Figures 5-10 show that in 5 patients with cirrhosis, the liver accumulated thyroxine weakly or undetectably; only the intestinal patterns showed well in these cirrhotic patients. Our data are insufficient to determine whether or not intestinal absorption of I-131 L-thyroxine is normal in cirrhosis.

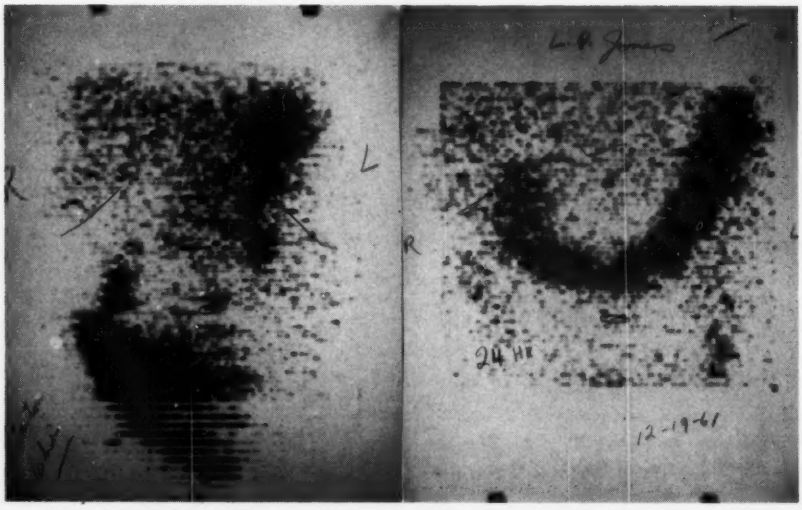

Figure 9 Figure 10

Fig. 10 refers to L. Q. J., 24 hours after the labeled hormone, only transverse colon was clearly outlined.

It appears as though possibly ⅓ of the thyroxine secreted from the thyroid may be concentrated in the liver and this is normally slowly released to the body or destroyed. In cirrhosis there was a very slight uptake of thyroxine by the liver.

Crude measurements of gamma radiation were made over the liver with a collimated Geiger-Muller tube 19.5 cm from the skin. Six hours after the thyroxine was administered, control patients had 28 ± 4 per cent of the thyroxine dose in the liver area and the effective half-life was 1-2 days. Similar measurements on the patients with cirrhosis showed 18 ± 7 per cent over the same area; no corrections were made for nonhepatic tissue. Therefore, crude uptake measurements were valueless as liver function tests but the liver scans were potentially valuable. The unsatisfactory nature of crude measurements in presence of a complex tissue background probably accounts for the fact that Triantaphyllidis *et al.* (12) reported only a slight accumulation of I-131 thyroxine in the liver of human beings.

The sensitivity of the scanning method was emphasized by patient M.B. in whom cirrhosis was suspected but no final diagnosis was made until a liver biopsy showed cirrhosis. Her usual liver function studies were normal, except for subnormal plasma albumin but her liver concentration of I-131 was severely impaired (Fig. 9).

DISCUSSION

These results may be helpful in understanding the metabolism of thyroxine in the body. Does the intestinal I-131 L-thyroxine arise from poor absorption or from resecretion via the bile? This question cannot be answered accurately from our data but Figure 4 shows no intestinal concentration after intravenous injection of labeled thyroxine. (This same patient, F. N., was also studied after oral I-131 thyroxine and his scan was similar to Fig. 3). Therefore, we favor the impression that approximately 30 per cent of L-thyroxine introduced into the digestive tract of man is not absorbed.

By what mechanism does thyroxine concentrate in the liver? This cannot be answered completely but evidently thyroxine binding globulin (TBG) must deliver continually 30 per cent or more of the circulatory thyroxine to a relatively large thyroxine pool in the liver. If the total I-131 thyroxine and its biological half-life were measured accurately in the liver, then possibly the amount of thyroxine used per day by the liver could be estimated and this compared with overall rates of utilization of thyroxine.

Another purpose of this study is to suggest that radiothyroxine may be a sensitive hepatic parenchymal cell function test. Such a test would be unique in that it would utilize a physiological quantity of a normal metabolite and in addition, important information regarding the hormone and iodine metabolism could be discovered. This method involves a small amount of radioactive material and oral administration is satisfactory. The bowel patterns are so clear that with some improvement, they might prove to be useful to study bowel functions and the site of absorption of important compounds. At present the scan procedure requires a tediously long time for the patient to lie under the equipment, but this will undoubtedly be improved. The greatest need for improvement is the quantitation

of the amount of thyroxine in the liver and in the intestine. It is suggested that this scanning procedure should be more thoroughly investigated to evaluate its usefulness.

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"Sephadex Chromatographic" Test in the Evaluation of Thyroid Function[1]

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INTRODUCTION

Thyroid function was evaluated by the "Sephadex Chromatographic" method (1, 2) in a total of 769 hospitalized patients. The results were compared with other thyroid function tests obtained on the same patients (3, 4, 5) and statistically analyzed (6) using the Chi-square criteria when applicable. From the analysis of the first 274 patients, the range of euthyroidism using the "Sephadex Chromatographic" method was 74 - 86. A standard deviation of 3.1 per cent was present with a mean normal value of 81.8. A reliability of 92 per cent reproducibility on repeat runs was observed for all determinations with or without addition of free iodide. Values above 86 were considered to be in the hypothroid range; those below 74, hyperthyroid. These ranges were obtained after analysis of the first 200 cases studied and have been re-evaluated and confirmed after 700 additional cases (within one standard deviation).

RESULTS

Table I compares "Sephadex Chromatography" with "24 hr. I-131 Uptake" (4) and "24 hr. protein-bound Iodine-131" (5) in 255 patients. By the use of the accepted ranges for thyroid function evaluation of these three tests, it was observed that in this group of 255 patients:

a. 19 patients gave results for one of these tests that was of different significance than were the results of the other two tests (which had given the same classification value—and coincided with the clinical evaluation).
b. Seven patients on which a clinical criteria was established gave for two of the used tests results in disagreement with the clinical evaluation (these two tests also disagreed among themselves).
c. No patient gave results for all of the 3 tests in which all three results were in disagreement with the clinical criteria.

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[1]Radioisotope Services of the Veterans Administration Hospital, Philadelphia; Albert Einstein Medical Center, Southern Division, Philadelphia; and Methodist Hospital, Houston, Texas.

TABLE I

SURVEY OF 229 SUBJECTS RECEIVING THREE THYROID FUNCTION TESTS: (A) I-131—24 HRS. UPTAKE, (B) PROTEIN-BOUND IODIDE,-131 (C) SEPHADEX G-25—I-131—T-3

Classification	*Positive for all three tests a, b, c*	*Positive for 2 tests (1 test is negative)*			*Negative for 2 tests (1 test is positive)*			*Negative for all three tests*	*Total*
		Negative for Uptake	*Negative for PBI-131*	*Negative for Sephadex*	*Negative for Uptake and PBI-131*	*Negative for PBI-131 and Sephadex*	*Negative for Uptake and Sephadex*		
Euthyroid	212	5	6	3	1	2	2	0	231
Hyperthyroid	12	1	1	1	0	1	0	0	16
Hypothyroid	5	1	0	1	1	0	0	0	8
Totals	229	7	7	5	2	3	2	0	255

TABLE II

THYROID FUNCTION SURVEY OF 226 SUBJECTS AS DETERMINED BY THE SEPHADEX G-25 METHOD VS. PBI-131 AND UPTAKE CRITERIA

Classification	*Positive by PBI-131 and Uptake Criteria*	*Sephadex G-25 criteria for the same 226 patients*		
		Euthyroid	*Hyperthyroid*	*Hypothyroid*
Euthyroids	198	187	8	3
Hyperthyroids	17	1	16	0
Hypothyroids	11	3	0	8
Totals	226	191	24	11

Table II presents the results of another group of 226 patients previously classified by:

a. "Clinical Criteria" (History and Physical)
b. "24 hr. I-131 Uptake" (4)
c. "24 hr. Protein-Bound Iodine-131" tests (5)

The results again indicated that by the use of the "Sephadex Chromatographic" test criteria, several patients previously called euthyroids may now be considered as hyperthyroids. This could be a "False positive" result. Yet two of these patients showed improvement when placed under suitable medications. Among the patients labeled hyperthyroids (except for one on thyroid therapy), all were confirmed as hyperthyroids by the "Sephadex" criteria. The number of hypothyroids patients studied in this group were too few for significant results from a statistical point of view.

TABLE III

THYROID FUNCTION SURVEY OF 769 SUBJECTS THAT RECEIVED BOTH RBC T-3 AND SEPHADEX G-25 TESTS, VS. UPTAKE AND CLINICAL CRITERIA

Classification	*I-131 Uptake and Clinical Criteria*	*RBC T-3 Test*		*Sephadex Test*	
Euthyroid □	728	720	710 □ 9 ● 1 ○	723	718 □ 1 ● 4 ○
Hyperthyroid ●	29	30	10 □ 19 ● 1 ○	37	9 □ 28 ● 0 ○
Hypothyroid ○	12	19	8 □ 1 ● 10 ○	9	1 □ 0 ● 8 ○
Totals	769	769	769	769	769

In Table III the results obtained from a group of 769 patients tested for thyroid function by both "Sephadex Chromatography" and "RBC-T-3 Absorption" (7) are presented. The judgment of thyroid function for this group of patients was made from a) "Clinical Criteria" (obtained by history and physical) and b) "24 hr. I-131 Uptake." (4). Statistical evaluation of the data (with a reliability of over 90 per cent) indicates that the "Sephadex" technique results in criteria equally as reliable as that from the "RBC-T-3" method in the evaluation of euthyroids. It is slightly superior for hyperthyroidism and as reliable in hypothyroidism.

SUMMARY

Statistical evaluation of the data indicates that the reliability of the "Sephadex Chromatographic" test as a criterion of thyroid function is statistically significant. It had an overall reliability of 88 per cent plus, as compared with other

thyroid function tests. When compared with the "RBC-T-3" Uptake test, it is equally reliable statistically (Chi-square rule) for euthyroid diagnosis, and slightly superior than this method for identification of hyperthyroidism. For hypothyroid criteria, the "Sephadex" test did not show as much reliability as did the "RBC-T-3" test.

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Radioautography, Principles and Procedures[1,2]

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It is of interest that one of the first known radioautograms ever intentionally made, in 1896, was part of the body of information which led the Curies to discover radioactivity (1). At this time, Henri Becquerel, in the pursuit of what he thought were studies in fluorescence phenomena, had exposed a film covered with black paper under an uranyl sulfate crystal, and upon development of the film observed the faint outline of the crystal. Of course, the true nature of the experiment became apparent after the Curies demonstrated the existence of radioactivity in uranium; and the first systematic use of radioautography was to search for radioactivity in minerals.

According to Boyd (2) the first biological application was performed by E. S. London in 1904 at the Imperial Institute of Experimental Medicine, St. Petersburg. In that year, London published one article in a French journal and two articles in Russian journals detailing his work and showing a whole-body radioautogram of a frog which had been exposed to radium emanations.

DEFINITION

The terms radioautography and autoradiography refer to any method by which the pattern of radioactivity contained in or on an object is accurately reproduced so that it may be visualized. The product of the technique is referred to as a "radioautogram." For the purposes of this discussion, attention will be confined to biological materials bearing radioisotopes, the distributions of which are to be visualized by photographic means at the microscopic level.

THE VALUE OF THE TECHNIQUE

Radioautography is superior to the counting methods for some types of biomedical research with radioisotopes. For instance, accurate determinations of

[1]This work was done under U. S. Atomic Energy Commission Contract AT(30-1)-901 with the New England Deaconess Hospital.

[2]Delivered in slightly different form at the Eighth Annual Meeting of the Society of Nuclear Medicine, June 14, 1961.

[3]From the Cancer Research Institute, New England Deaconess Hospital, Boston 15, Massachusetts.

the sites of deposition of some isotopes in organs, tissues, cells, and parts of cells, can be made by means of radioautography. It is also possible to estimate the relative quantities of radioisotope in the various parts of a tissue or cell. Occasionally amounts of radioisotopes which will barely record on a Geiger-Mueller or well-type scintillation counter will yield useful information by radioautography since the photographic film can integrate the incident radiation over a much longer time than is practical with Geiger-Mueller or scintillation counting. Furthermore, accurate counting of radioisotopes in tissues requires the destruction of the tissue either by ashing, dissolving in acid or alkali, or homogenizing. This is not necessary with radioautography where the tissue, or at least the histological preparation, remains intact and may be correlated with the pattern of the radioautogram.

The usefulness of and interest in radioautography is further attested to by the great amount of literature which has accumulated as witness the bibliographies of Passalaqua (3) and Johnston (4).

Principles

Photographic Considerations

Photochemistry

Since the photographic emulsion is the recording device upon which so much depends, it would be well to become familiar with its characteristics insofar as they affect the technique. All monochrome film emulsions consist of mixtures of gelatin and crystalline silver halides, primarily the bromide. Slight imperfections in the crystal lattices are created by introducing trace quantities of sulfide during the manufacture of the halide. These imperfections, formerly called sensitivity specks but now known as electron traps, react to the passage of energy of nearly any kind by concentrating electrons. When this happens, the positive silver atoms in the vicinity are attracted and migrate to the negatively charged volume. These altered grains of silver halide constitute the "latent image" as long as they remain concentrated. The process of development consists of immersing the film in a solution which reduces silver halide to metallic silver. The kinetics of the reaction are such that the crystal grains containing the concentrated silver atoms are reduced much more rapidly than the unaffected grains. By controlling the length of contact, one can then arrange that the energized grains are reduced while only a very few other grains will be reduced. The unreduced grains would ultimately become reduced, but they are subsequently dissolved out of the emulsion by the hypo solution which dissolves the silver halide much more rapidly than the metallic silver.

Nuclear Emulsions

The desirability of intercepting as much radiation as possible and the requirement of high resolution have made the production of special emulsions necessary since ordinary emulsions are not made to satisfy these requirements. Ordinary emulsions contain about 30 per cent silver halide by weight and have

a relatively large grain size. Nuclear emulsions contain up to 90 or 95 per cent silver halide, and the grain size averages 0.2 to 0.3 micra with a maximum size of 0.5 micron. X-ray film has a grain size which varies between 0.5 and 6 micra. The larger grain size yields higher sensitivity but lower resolution. The nuclear emulsion achieves sensitivity by the higher silver halide content and gives excellent resolution due to the small grain size.

The response of the emulsion to radiation depends to a large extent upon the characteristics of the radiation traversing it. Alpha particles which have a large mass and move relatively slowly give up their energy to atoms in or near their path but do not tend to be deflected from an approximately straight course; therefore, passage of an alpha particle through the emulsion results in a fairly straight line defined by a series of silver granules further apart at the origin than at the end of the path. The track may actually consist of a cylinder composed of granules if the local ionization is sufficient in quantity. The track of a beta particle is much more complicated since it has little mass and is easily deflected by atoms in its path. The beta track is tortuous, and the individual granules composing it are relatively far apart. It is impossible to unravel a group of beta tracks if they pass through a small volume. X or gamma rays, which are very fast and of negligible mass, register in nuclear emulsion by eliciting secondary electrons. For this reason, X-ray films are thickly coated, usually on both sides, and are often used in conjunction with screens which scintillate under irradiation. The larger size of the silver grains also increases the interception of the rays. X-ray films are more sensitive than nuclear emulsions by a factor of 100 but yield poor resolution.

Types of Emulsion Available

Nuclear emulsions are now available from Eastman Kodak (USA), Kodak, Ltd. and Ilford, Ltd. of England in a variety of forms. Eastman Kodak provides nuclear emulsions in a variety of sensitivities and thicknesses coated on glass plates the size of microscope slides in several thicknesses with and without a gelatin protective coating. In order of ascending sensitivity these emulsions are designated: NTA, NTB, NTB2 and NTB3. NTB2 and NTB3 are the most commonly used in biological work. These emulsions may also be obtained in bulk form. Kodak also supplies stripping film in several forms. Kodak, Ltd. supplies several types of emulsion of which their AR10 stripping film is quite popular in this country and is now being distributed by Eastman Kodak, but it is not available in bulk. Ilford G5 and other emulsions are available as stripping film or in bulk. When not in use, nuclear emulsion should be stored at 5°C. It will keep up to six months or longer if not exposed to too much radiation. The ways in which the various forms of nuclear emulsion are utilized will be discussed below.

BIOLOGICAL CONSIDERATIONS

Selection of Radioisotope

Physiological, biochemical or metabolic factors determine the isotope which will be used: radioiodine for thyroid studies, tritiated thymidine for DNA and/or

cell reproduction studies, radioiron or radiochromium for erythrocyte studies, radiostrontium or radiocalcium for bone, etc. If one has a choice of isotope, one should select a highly ionizing one with a reasonable path length in tissue and emulsion. The low-energy isotopes such as tritium and carbon 14 which yield excellent resolution are more difficult to work with because of the limited range of their radiations in tissue and emulsion. The range in tissue is about three to four times that in emulsion. Herz (5) and Yagoda (6) have published extensive fundamental treatments of the interactions of radiation and nuclear emulsions.

The method of administration of the isotope and the length of time before sacrifice of the animal will be determined by the special experimental conditions under which one is working. Little can be said about this except that the length of time between administration of isotope and the removal of tissue for radioautography ought to be short relative to the half life of the isotope whenever possible. This is also true of the time spent in the necessary histological processing. However, successful radioautography can sometimes be done when several half lives have elapsed between isotope administration and the application of the nuclear emulsion.

Histological Processing

In general, ordinary histological methods including staining are applicable with the proviso that the reagents used do not dissolve the radioisotope-labeled compounds in the tissues. Obviously any significant degree of leaching of the isotope-bearing compound operates against the resolution and specificity of the technique. Indeed, it may eliminate any usefulness the technique may have.

The usual fixatives are normally satisfactory for radioautography; if they are not suitable, one can use freeze-dry (7), acetone (8) or other fixatives which may have to be specially developed for the purpose at hand. If embedding in paraffin is contraindicated, embedding in water-soluble carbowax can be done (9). Tissues should be sectioned as thick as the cytological resolution required will permit, so that each section will contain as much isotope as possible.

If staining is done before the emulsion is applied and the tissue is not sealed by a protective layer, the subsequent photographic development will often result in decolorization of the stain. If medium or high-energy emitters are being used, it is possible to add a protective layer by dipping the slides in celloidin, formvar, or nylon after staining and before applying the emulsion (10). This will seal off the stained tissue and protect it from being affected by the photographic processing. The protective layer has an additional advantage in that it prevents pseudoradiographic effects on the emulsion due to reducing substances which may be present in the tissue.

Unfortunately, tritium is such a weak emitter that even a one micron thick protective coating will greatly reduce the amount of radiation which can reach the emulsion. For this reason and because anything interposed between tissue and emulsion reduces resolution, it is usually preferable not to use a protective layer but to stain after the radioautogram has been photographically processed. Staining will be discussed in detail below.

To determine if radioisotopes are being leached from the tissue, the reagent or reagents used may be evaporated to a small volume and the amount of radioactivity measured in an appropriate counter. If a significant number of counts result, the reagent must be changed to one which does not dissolve the isotope. Even if no counts are found, it is well to be aware that some minor shifting of the radioisotope may occur in the tissue.

PROCEDURES

While there are probably as many ways of doing radioautography as there are radioautographers, there are five basic techniques. More detailed information and references are available in Boyd (2) and in the bibliographies already mentioned (3, 4).

1. *Apposition*

The first and simplest of all the techniques may be called the apposition method. In this technique the specimen is positioned on a cut film or a plate film protected from light and exposed, usually under pressure to obtain close contact. After exposure, the specimen is separated from the film and the film developed. The main drawbacks to this method are that it is very difficult to correlate the radioautographic image with the specimen at the microscopic level once the two are separated, and resolution is not as good as it might be.

2. *Mounting*

The next technique to be evolved is known as the mounting technique. This technique consists of mounting the biological specimens directly on a nuclear emulsion plate or cut film instead of the usual glass slide which has the advantage that the tissue remains in constant relation to the image. This is achieved in a variety of ways; mounting the paraffin ribbon directly, which has the drawback that the sections are usually quite wrinkled; mounting the ribbons by floating them on a warm water bath so that they smooth out and then dipping the nuclear plate under them and carrying them out of the bath, which has the disadvantage that the radioisotope may dissolve out in the water bath; and, lastly, smoothing the individual sections by gently heating and blowing on them before mounting on the nuclear plate, which has the disadvantage of being very painstaking and slow. The technique also suffers from the drawback that the emulsion must be processed through the tissue.

3. *Stripping Film*

The next step in the evolution of these techniques was the very ingenious idea of Pelc (11) of reversing the mounting technique and mounting the nuclear emulsion on the specimen. This is done by detaching or "stripping" the nuclear emulsion from the temporary glass or acetate support upon which it is placed by the manufacturer and floating it on a water bath. The specimen is then dipped under it very much as the nuclear plate was dipped under the specimen in the

mounting method. When the emulsion has dried it usually adheres quite tightly to the slide and specimen because it shrinks as it loses water. In this method resolution is excellent, and the radiographic image retains its orginal relationship to the specimen. The problems with this technique are the difficulty most people encounter in handling the thin unsupported emulsion, it is time consuming, and there is the possibility of radioisotope loss in the water bath.

4. *Coating Technique*

The next modification was originated by Bélanger and Leblond at McGill in 1946 (12). Unexposed emulsion was scraped from soaked lantern plates, melted and painted over tissue specimens with a brush. This had the great advantage that the fluid emulsion conformed intimately to the contours of the specimen thus assuring good resolution and close registration of image and tissue. This method is difficult because of bubble formation during brushing and the variability of the thickness of the emulsion layer which is quite important if estimates of relative content of radioactivity are to be made.

5. *Dipping Technique*

The most recent modification, published in 1955 (13), is a variation of the coating technique. In 1953, bulk nuclear emulsion had been made available by Eastman Kodak for experimental use, mostly for coating. While trying to make bubble-free coated radioautograms, it occurred to this author that the technique could be improved by simply dipping the slides into a quantity of the melted bulk emulsion and wiping the excess emulsion off the bottom of the slide. This method eliminates the bubble problem. One must exercise care to obtain even layers, but it can be done. All the advantages of coating are retained with the bonus of great simplicity, ease and speed in the preparation.

For some special purposes, one of the first four methods described may be preferred, but for general use with slide-mounted histological preparations, the dipping method is best. Since this technique is rapid, universally applicable, works well with alpha and beta particles at all available energies, is flexible, is capable of high resolution and very easy to perform, it will be described in detail. It is a good method for a beginner and is also perfectly suitable for use by the most advanced radioautographer.

Detailed Procedure

If it is feasible, the mounted tissues should be rehydrated after deparaffinization. This step will aid in obtaining even layers of emulsion which adhere well to the tissue and glass.

While the tissue slides are going through the last stages of processing, the container of bulk nuclear emulsion is taken from the refrigerator and placed in a water bath in the darkroom and warmed to 40°C. If thinner emulsion layers are desired, the temperature may be raised but not above 50°C (to avoid heat sensitization artifacts). When the emulsion is at the predetermined temperature

and the slides are ready, the slides are taken from the water in which they were rehydrated and arranged in a convenient place where they may be easily grasped at the labeled end in the dark. If too many slides are removed at once, the last ones to be done will dry and may lose some cytological detail. Groups of ten are convenient. The room is darkened and the series 1 or 2 safelight turned on. The cover is removed from the emulsion container, and a clean glass rod is used to stir the emulsion thoroughly but gently without introducing bubbles. Stirring is necessary to maintain proper distribution of the silver halide in the gelatin. Once the stirring is completed, the first slide is picked up and immersed long axis vertical so that the tissue goes about half an inch below the surface. It is immediately withdrawn and allowed to drain for a few seconds to a minute onto a gauze pad held in the other hand. Within limits, the longer the drainage, the thinner the emulsion layer and the better the resolution. With ten second drainage, dry layer thickness will be about five micra. Emulsion must not be allowed to drain back into the container. After draining, the gauze pad is used to remove all emulsion from the bottom of the slide. The slide is then placed horizontally in a tray to gel and be exposed. The slides need be kept horizontal no longer than the ten to twenty minutes it takes the emulsion to gel. The slide may then be placed in any suitable position. When the tray is full, it is placed in an exposure chamber specially made for the purpose (14) and other trays used if necessary. The proper compartments of the chamber are then charged with Drierite and solid CO_2, and the cover is sealed on. The chamber seals itself by means of an oil valve after all the CO_2 has sublimed. As the gas evolves, it is passed through the chamber in such a manner that the air is forced out completely.[1] If these precautions to eliminate oxygen and reduce moisture below 15 per cent relative humidity are not taken, serious losses of latent image may occur during the exposure period.

Many experienced radioautographers still insist on exposure around 5°C or even lower and show excellent results as proof of the necessity for low temperatures. Actually, the formation of the latent image is an electrochemical process; and, therefore, lowered temperatures interfere with latent image formation. Lowered temperature effectively reduces emulsion sensitivity. The explanation of success at low temperatures is that the low temperature also reduces latent image fading, since the fading is itself an electrochemical process. Furthermore, the atmosphere in a cold storage area is generally very dry due to condensation and freezing out of moisture, and dryness is also conducive to preserving the latent image. It has been proposed that less fogging occurs at low temperatures. In reality, the reduction of fog is due to the reduced sensitivity of the emulsion, and the ratio of useful image to fog probably remains the same. With the dipping technique, fog is very seldom a problem; and, therefore, it is best to expose at room temperature to obtain more of the useful image. The fog level averages three to five grains per 100 μ^2 in this laboratory. However, the dipping technique

[1]The complete equipment for the dipping technique, consisting of an exposure chamber and the necessary ancillary equipment, is available from Controls for Radiation, Inc., 130 Alewife Brook Parkway, Cambridge 40, Mass.

is perfectly amenable to low temperature exposure; and should an investigator prefer to do so, or if there is an experimental reason for it, the exposure box may be placed in a cold room after it has been sealed.

Exposure time varies according to sensitivity of the emulsion, the total dose of isotope administered, its biological half life, the length of time between administration and sacrifice of the animal, the degree of concentration, the pattern of distribution in the tissues under study, the thickness of the tissue section and the energy of the radiation. These factors are difficult to reduce to a formula which could indicate actual exposure times. It has been found simpler to use replicate slides and to develop a few at intervals of several days until optimum exposure times become apparent. One soon gains sufficient experience to estimate the initial exposure period.

When the initial exposure period has elapsed, photographic development is performed with ordinary glass staining dishes containing the developing solutions. Ten to twenty slides are placed in the usual glass staining rack for immersion in the solutions. The solutions used are Kodak D 19 developer, Kodak SB5a stop bath and Kodak Fixer. D 19 is a rapid, fine grain, fairly stable developer in wide use in radioautography. The SB5a stop bath is nonswelling thereby reducing the probability of dimensional changes and silver grain shifting. The acid fixer hardens the emulsion layer as it fixes which helps prevent damage to, or loss of the emulsion layer during washing or subsequent handling.

The photographic processing schedule is as follows:

Kodak D 19 Developer	1 to 10 min.
Kodak SB5a Stop Bath	15 seconds
Kodak Fixer	2 x clearing time
Wash	0.5 to 1 hr.

All solutions should be 18°C ± 1. If the individual solutions vary appreciably in temperature, the likelihood of reticulation increases. Higher temperatures increase the likelihood of the emulsion layer washing off. After the slides have been in the fixer for a minute, sufficient white light may be used to observe the time it takes to clear the emulsion, and then the slides should be left in the fixer for an additional period equal to twice the clearing time. Thorough washing in running tap water at 18°C removes all the fixer and insures that no image loss or crystallization of hypo will occur if the preparations are stored for long periods.

If the tissue has not been stained previously, staining is now performed. Certain stains, such as eosin and acid fuchsin, are taken up by the gelatin of the emulsion so strongly that it is difficult to study the specimens properly after staining. However, others such as hematoxylin, polychrome toluidine blue, metanil yellow, gallocyanin, lithium carmine and alum cochineal are reported to be useful and do not overstain the gelatin. If hematoxylin-eosin staining is required, it can be achieved by eosin staining before dipping and hematoxylin staining after photographic processing. The eosin is not decolorized during de-

velopment, but hematoxylin is. However, hematoxylin does not stain the emulsion objectionably so that staining afterward is quite feasible. By this maneuver, perfectly acceptable hematoxylin-eosin preparations can be made. In our laboratory toluidine blue is used routinely with excellent results.

The routine is as follows:

1. Stain in one percent toluidine blue directly from wash water, 30 sec;
2. Destain in 70 per cent ethanol until gelatin is clear and tissue is desired shade;
3. Dehydrate in two changes of 100 per cent n-butanol;
4. Clear in three changes of xylol;
5. Soak in 1/2 xylol and 1/2 balsam for one hour up to 24 hours or until preparations are clear;
6. Mount in balsam under number 1 cover glass.

The very low humidity during the exposure period may cause a great loss in the visible cytological detail. This can be overcome by using sufficient length of time for step number 5. If the xylol step is omitted, the toluidine blue will be bleached in a few weeks.

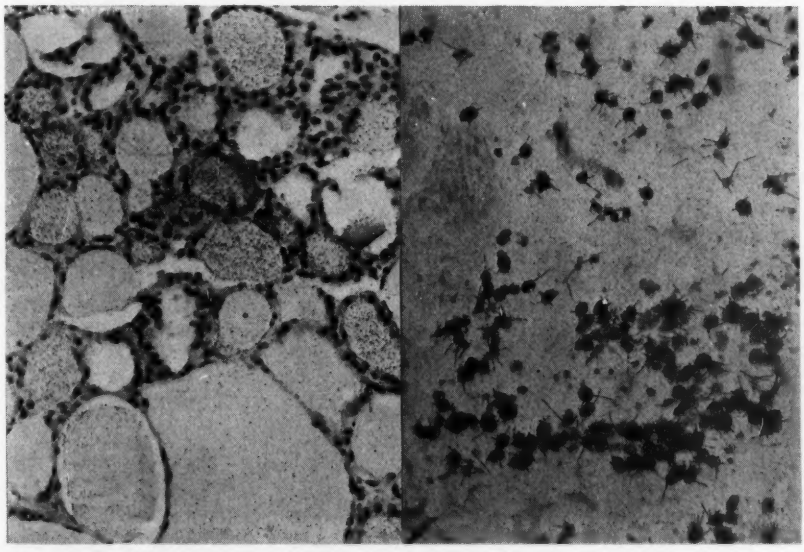

Fig. 1. Photomicrograph of radioautogram of mouse thyroid. 250 X, H. & E. stain. Ten microcuries of I 131 injected 24 hrs. prior to death. Two-day exposure. Note differential storage in follicles.

Fig. 2. Photomicrograph of radioautogram of human neck tumor tissue near site of leakage of thorotrast injection 18 years previously. Two-week exposure. 250 X, toluidine blue stain. Note alpha tracts originating from nests of macrophages.

Study and Photography

The radioautograms prepared this way can be studied under the microscope as ordinary histological preparations. Under low and high dry magnification, slight adjustment of the fine focus enables one to correlate the histologic with the radioautographic image. Oil immersion requires somewhat greater adjustment of focus. Similarly, photomicrography is quite simple under the lower magnifications by using a compromised focus, but it is necessary to make two negatives if oil immersion magnification is required because the focal plane is too thin to focus clearly on both the tissue and the emulsion layers at once. A very simple registration frame suggested by Hoecker and described in Boyd (2) makes possible very accurate registration of the negatives for printing. Thus, study and recording of the data obtained by radioautography is simple.

Grain Counting

There is some question as to whether the emulsion layer of a radioautogram prepared by dipping is sufficiently even to permit grain counting. Leblond (14, p. 137) claims that it is if the slide is rapidly dried in an oven at 40°C. For low energy isotopes such as tritium and C-14, the question is academic, if the thinnest

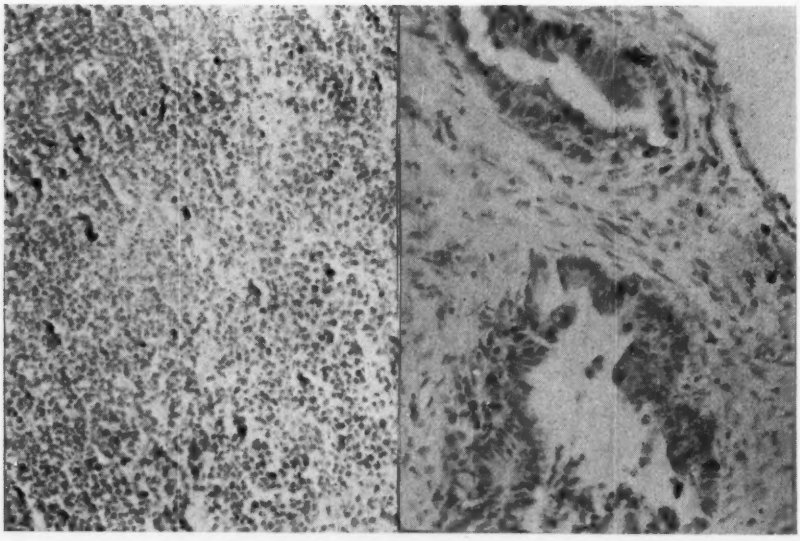

Fig. 3. Photomicrograph of radioautogram of lymph node of a rat sensitized to human serum albumin and then challenged with radioiodine-tagged albumin. One-week exposure. 250 X, H. & E. stain. Note variation in antigen fixation.

Fig. 4. Photomicrograph of radioautogram of human carcinoma of the colon. Tissue incubated with tritiated thymidine 5 μc/ml for two hours immediately after removal. 250 X, hematoxylin stain. One-week exposure. Most cells have lost ability to take up tritiated thymidine.

part of the emulsion layer is thicker than the maximum range of the beta particle. In this case grain counting may be performed with confidence since no radiation can be "lost" through the thin areas. In effect, the emulsion is uniformly available as far as the radiation is concerned, and, therefore, may be considered to be present as a uniform layer.

Controls and Artifacts

Each slide should be used as its own control by observing the number of developed silver granules in natural or artifactual tissue spaces as well as in areas relatively remote from the tissue. In evaluating the slides this background is subtracted. It is also necessary to use nonradioactive control tissue slides when protective layers are not used in order to account for silver granules which may be due to the presence of reducing substances such as sulphydryl compounds or even reducing reagents which have not been completely washed out of the tissues. Other sources of background are: cosmic rays, naturally occurring radioisotopes in the containers, slides and tissues, irradiation of emulsion during immersion of the radioisotope-bearing tissue, mechanical factors and heating. From time to time blank slides should be included to check the fog level of the emulsion, and when it gets too high, the emulsion should be discarded.

CONCLUSION

In conclusion, it can be said that the dipping method of radioautography is simple and flexible. Modifications may be used depending on experimental conditions. Successful modifications will result in high-grade radioautograms. Figures 1 through 4 are examples of the varied applications of the technique.

ACKNOWLEDGMENTS

The author gratefully acknowledges the excellent technical assistance of Mrs. J. M. Thurston. Drs. L. McDonald and L. Lieb kindly permitted the use of the photomicrographs in Figures 3 and 4 respectively, which were prepared in this laboratory.

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Announcement to Authors

Preliminary Notes

Space will be reserved in each issue of THE JOURNAL OF NUCLEAR MEDICINE for the publication of one preliminary note concerning new original work that is an important contribution in Nuclear Medicine.

Selection of the preliminary note shall be on a competitive basis for each issue. One will be selected after careful screening and review by the Editors. Those not selected will be returned immediately to the authors without criticism. Authors may resubmit a rejected or revised preliminary note for consideration for publication in a later issue. The subject material of all rejected manuscripts will be considered confidential.

The text of the manuscript should not exceed 1200 words. Either two illustrations, two tables, or one illustration and one table will be permitted. An additional 400 words of text may be substituted if no tables or illustrations are required. Only the minimum number of references should be cited.

Manuscripts should be mailed to the Editor, Dr. George E. Thoma, St. Louis University Hospital, 1325 South Grand Blvd., St. Louis 4, Missouri. They must be received before the first day of the month preceding the publication month of the next issue, e.g., preliminary notes to be considered for the May, 1963 issue must be in the hands of the Editor before April 1, 1963.

JOURNAL OF NUCLEAR MEDICINE 4:155-158, 1963

A Chromatographic Study of the Stability of Iodine-131 Labeled Sodium o-Iodohippurate

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A series of experiments have been carried out in order to study the stability of sodium *o*-iodohippurate (Hippuran) labeled with iodine. Solutions of sodium *o*-iodohippurate I-131 in pharmaceutical form are widely used as a radioisotopic diagnostic agent in kidney function studies.

The purpose of the experimental work was to determine the stability of the radioactive material under various conditions of pH, salt concentration, and time.

Assays were carried out using sodium *o*-iodohippurate labeled with I-131 by exchange (1). Preparations possessing different specific activities were tested in order to determine the effect of specific activity on the rate of decomposition of the product.

EXPERIMENTAL

A chromatographic procedure was used to determine the amount of iodide liberated by break down of the initially iodide-free material. Descending chromatography, using a N-butanol-acetic acid-water (4:1:1 v/v), was employed. Under the conditions employed, the R_f found for sodium *o*-iodohippurate was 0.82-0.86 and for iodide 0.09-0.14.

The extent of decomposition was determined 10, 20, and 30 days after the date of preparation using sodium *o*-iodohippurate preparations initially possessing specific activities of 0.05, 0.20, and 2.0 mc/mg.

The effect of solution pH on stability was also studied. Original solutions of sodium *o*-iodohippurate containing 0.9 per cent of benzyl alcohol and 0.2 per cent of sodium citrate possessed a pH of 8.0. Solution pH was altered to 10.0, 2.0, and 7.0 by the addition of 0.04 ml of 0.1 N NaOH, 0.1 N HCl, or phosphate buffer (pH 7.0) to 0.1 ml of the original solution stored in a plastic container. The effect of solution pH on the liberation of free iodide is shown in Table I.

The same technique was employed to study the effect of salt concentrations on the stability of high specific activity (2 mc/mg) sodium *o*-iodohippurate. The

[1]Volk Radiochemical Company.

TABLE I

FREE IODIDE RELEASED AFTER STORAGE OF SODIUM O-IODOHIPPURATE AT DIFFERENT PH VALUES

		Per Cent Activity in the Iodide Chromatographic Spot		
mc/mg	*pH*	*10 Days*	*20 Days*	*30 Days*
0.05	2.0	4.0	4.1	6.2
	7.0	4.8	4.8	6.2
	8.0	2.4	2.8	3.4
	10.0	4.1	4.7	5.8
0.2	2.0	4.8	6.4	10.1
	7.0	5 1	7.2	11.3
	8.0	4.1	6.2	10.3
	10.0	5.2	8.2	10.3
2.0	2 0	18.0	18.3	18.3
	7.0	16.4	22.7	31.0
	8 0	13.2	20.6	20.8
	10.0	18.1	23.4	28.7

effects of sodium chloride concentrations of 0.33, 0.82, 1.65, 3.33, and 8.25 per cent on the stability of sodium *o*-iodohippurate solutions are summarized in Table II.

Table III indicates the effect of light on the stability of high specific activity sodium *o*-iodohippurate. A "stabilized solution" of 2 mc/mg sodium *o*-iodohippurate in a sealed serum vial was exposed continuously for 10-, 20-, and 30-day intervals to the light from a "cool white" 40 watt fluorescent lamp at a distance of 10 centimeters.

In order to achieve better separation of the possible compounds formed in the break down of sodium *o*-iodohippurate, a two-dimensional chromatograph was prepared employing two separate solvent systems. The test material was applied as a small (4 mm) diameter spot at one corner of a chromatographic filter paper sheet. The spot was initially developed in the ascending manner using N-butanol-acetone-water (5:5:1 v/v). After drying, the sheet was rerun at 90° from the initial solvent direction using N-butanol-acetic acid-water (4:1:1

TABLE II

FREE IODIDE RELEASED AFTER STORAGE OF SODIUM O-IODOHIPPURATE WITH DIFFERENT SALT CONCENTRATIONS

	Per Cent Activity in the Iodide Chromatographic Spot		
NaCl %	*10 Days*	*20 Days*	*30 Days*
0.33	14.1	17.8	19.4
0.82	5.9	6.0	10.3
1.65	4.9	8.0	15.6
3.33	3.0	8.0	14.3
8.25	3.5	5.6	13.8

TABLE III

FREE IODIDE RELEASED AFTER STORAGE OF SODIUM O-IODOHIPPURATE WITH AND WITHOUT LIGHT EXPOSURE

	Per Cent Activity in the Iodide Chromatographic Spot	
	With Exposure	*Without Exposure*
10 Days	17.6	7.0
20 Days	22.7	20.6
30 Days	37.1	20.8

v/v). After the removal of the second solvent, a radioautograph was obtained by placing the chromatographic sheet in contact with Gevaert No. D 4 industrial x-ray film, obtaining the radioautograph shown in Figure 1. The identity of the

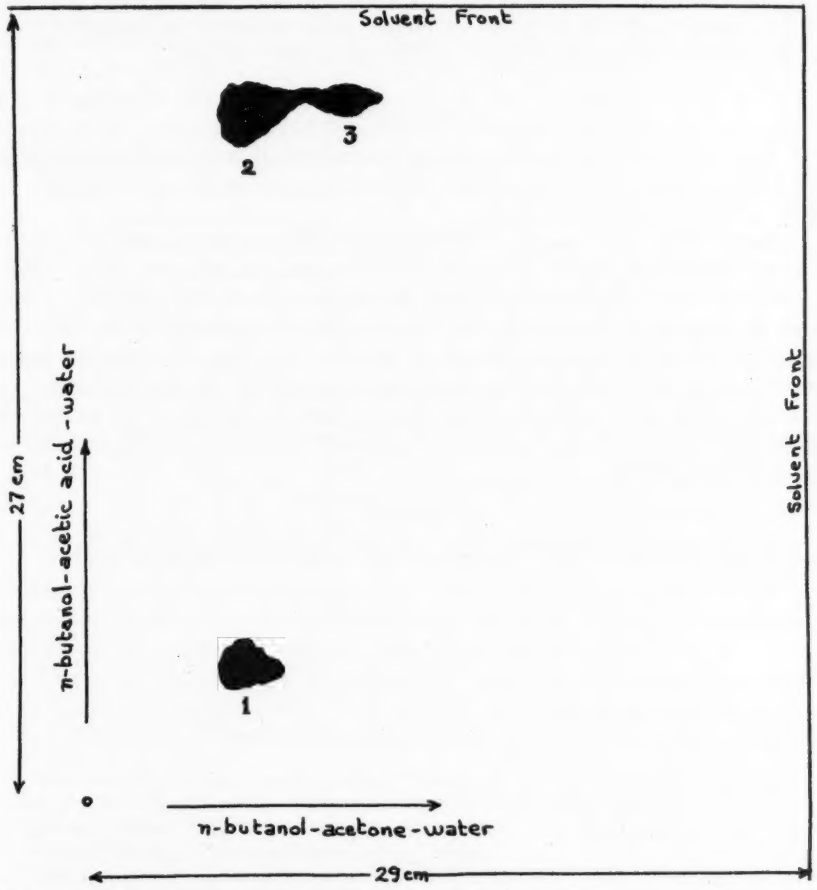

Fig. 1.—Two-dimensional chromatograph, sodium o-iodohippurate.

radioactive spots was determined by comparison of their measured R_f's to those obtained using known materials under the same experimental conditions. After locating the areas possessing radioactivity, these were cut out of paper chromatogram, and their respective activities determined using a scintillation counter.

The ratio of the radioactivity of each area to the radioactivity initially applied is as follows: Spot 1 (iodide), 21.8 per cent; Spot 2 (sodium *o*-iodohippurate), 66.5 per cent; and Spot 3 (an unknown compound, possibly related to sodium *o*-iodohippurate), 11.7 per cent. The value for radioiodide released after 30 days corresponds well with the value obtained by one-dimensional chromatography for free iodide released from high specific activity sodium *o*-iodohippurate solution stored for 30 days. (See Table I.)

Attempts were made to identify the unknown compound constituting Spot 3. Results of tests using ferric chloride, diazotized *p*-nitroaniline, and phenolphthalein to possibly identify a free phenolic group were negative. Tests using *o*-phenylenediamine and semicarbazide, for keto acids, were also negative. The ninhydrin reaction for identification of amino acids similarly was negative, both for the material isolated in this spot and for the original mixture.

DISCUSSION

The results of these experiments seem to indicate that the stability of iodine-131 labeled sodium *o*-iodohippurate solutions decreases as the initial specific activity of the product is increased.

The stability of sodium *o*-iodohippurate solutions seems greatest at pH 8.0. The presence of appreciable concentrations of sodium chloride in sodium *o*-iodohippurate solutions appears to partially protect them from decomposition. A possible explanation is that the sodium and chloride ions present in the solutions minimize the effect of beta particles emitted by the iodine-131 bonded to the aromatic ring, which may be the primary agent in effecting the breakdown.

The effect of exposure to light (the photoelectric effect) is not of greater magnitude than the effect of altered pH, at least with high specific activity sodium *o*-iodohippurate.

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JOURNAL OF NUCLEAR MEDICINE 4:159-161, 1963

The Excretion of Na^{22} in Sweat[1]

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C. J. Hlad, Jr., M.S., and E. Miller, M.S.

Denver

INTRODUCTION

The three most common features of cystic fibrosis of the pancreas are: Severe chronic lung disease, positive family history, and elevated sweat electrolytes. The incidence of cystic fibrosis of the pancreas is reported to be one in every 1,000 live births (1). It is thought to be transmitted by a recessive semilethal gene. The peak mortality is at four years of age and less than 20 per cent of the cases survive beyond 10 years of age (2). Death is usually the result of respiratory insufficiency or pulmonary infection. It is perhaps mere coincidence that the estimated incidence of the population which carry the heterozygous gene for cystic fibrosis of the pancreas is 5 per cent and the incidence of significant obstructive emphysema at autopsy is also 5 per cent (2, 3).

Increased sweat concentration of sodium and chloride in patients with cystic fibrosis of the pancreas were first described in 1953 (4). At that time total body sweat was collected by wrapping the subject in a plastic sheet and blankets. In 1959 Gibson and Cooke described the collection of sweat samples by iontophoresis (5). This method is simple and remains the method of choice.

Recently several papers have reported the incidence of elevated sweat electrolytes in patients with certain forms of chronic lung disease to be about 25 per cent (6, 7, 8). These patients are similar to the relatives of cystic fibrosis patients in that many have elevated sweat sodium and chloride values, and that they show a response to stress or salt deprivation. Patients with cystic fibrosis are unable to conserve their sweat electrolytes. It has been postulated that a portion of chronic lung disease in adults is related to the heterozygous state of cystic fibrosis, analagous to sickle cell anemia or Mediterranean anemia.

A major unsettled question is what constitutes normal sweat electrolytes in adults. Most authors have either found or assumed that normal adults have sweat electrolytes similar to normal children. One exception is a report that normal adults have higher sweat electrolytes than normal children (9).

This paper describes a new method for measuring the excretion of sodium in sweat, and reports the results of its application in control subjects, in patients with chronic lung disease and in patients with cystic fibrosis of the pancreas.

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METHODS

Fifty adult hospital patients without chronic lung disease, or family history of chronic lung disease, or evidence of adrenal disease and a normal salt intake were selected as control subjects. Twenty adult patients with chronic lung disease were studied; thirteen of these had advanced emphysema and seven had either severe asthma or cylindrical bronchiectasis. Four patients with proven cystic fibrosis of the pancreas were studied.

The test procedure utilized radioactive Na^{22} which has a physical half-life of 2.6 years and a biological half-life of two weeks (10). A dose of 0.15 μc/kg of body weight was given orally and sweat collected 12-18 hours later. It has been shown that radioactive sodium comes in complete equilibrium with exchangeable body sodium in a minimum of three hours and a maximum of ten hours (11, 12). Sweat was collected by iontophoresis (5). Electrodes were placed on the forearm with pilocarpine on a piece of gauze under the positive electrode and saline on gauze under the negative electrode. A current of three milliamps was applied for ten minutes followed by thorough cleansing and drying of an area on the volar surface of the forearm. Then a preweighed piece of gauze was applied to the area, covered with plastic, and sealed with tape. The forearm was exposed to a constant temperature of 100° F. for thirty minutes. The gauze was removed with forceps, replaced in a vial, and reweighed to obtain the weight of sweat.

Sweat weights varied from 0.1 to 1.0 gm. The vial containing the sweat soaked gauze was placed in a well type scintillation counter and counted for 20,000 counts. A 1 ml sample of serum drawn during the sweat collection was similarly counted. Results of the test were expressed as an R value which represented the counts per miunte per gram of sweat, divided by the counts per minute per ml serum expressed as a percentage. For comparison, a sweat chloride determination was done by the titration method of Schales and Schales (13).

RESULTS AND DISCUSSION

Table I is a summary of the results in the 50 normal patients, the 20 patients with chronic lung disease, and 4 patients with fibrocystic disease of the pancreas. The Na^{22} test shows a clear cut differentiation between the control group and the patients with pancreatic fibrosis. The results in patients with lung disease fall

TABLE I

	No. of patients	*R** *Mean ± S.D.*	*Range*	*Sweat Chloride* *Mean ± S.D.*	*Range*
Control	50	25.1 ± 9.4	8–41	17.7 ± 13.3	1–58
Chronic Lung Disease	20	32.0 ± 21.2	9–75	37.3 ± 33.1	10–115
Significance		p = .06		p = .001	
Fibrocystic Disease	4		57–85		74–129

*R = Sweat Na^{22}/Serum Na^{22}

between the control group and the patients with pancreatic fibrosis. The difference between the controls and the patients with lung disease is significant at the 6 per cent level. The sweat chloride results follow a similar pattern, but here the difference between the controls and the patients with lung disease is highly significant.

The Na^{22} sweat test is simple and gives results which parallel the chloride test. Its sensitivity seems to be less than that of the chloride test. The observation that some patients with chronic lung disease have abnormally high sweat electrolytes has been confirmed.

SUMMARY

A new method for measuring sodium excretion in sweat, utilizing Na^{22} is described. The physical characteristics of the radioisotope are very favorable and the test procedure is simple. The method has been applied to 50 control subjects, 20 patients with chronic lung disease, and 4 patients with fibrocystic disease of the pancreas. The results show a significant elevation of sweat Na^{22} excretion in patients with chronic lung disease, but not to the degree seen in patients with cystic fibrosis of the pancreas. These findings are compatible with the concept that some patients with chronic lung disease may have a form of pancreatic fibrosis not clinically detectable.

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JOURNAL OF NUCLEAR MEDICINE 4:162-166, 1963

Radioiodine Uptake Studies in Newborn Infants[1,2]

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INTRODUCTION

Radioisotope laboratories are frequently asked to perform and intepret thyroidal iodine uptake studies in young children and infants. Interpretation of results has been difficult because of conflicting reports in the literature concerning euthyroid iodine uptake values in newborn infants. To date we have been aware of only four published studies in the thyroidal uptake of radioiodine in newborn infants. Van Middlesworth (1) in 1954 reported on the thyroidal iodine uptake following the intramuscular injection of 1 microcurie of I-131 into seven male newborn infants from one to three days old. At 24 hours, the uptake of I-131 by the thyroid was from 61 to 94 per cent of the injected dose. He concluded that the newborn infant may experience a period of physiologic hyperthyroidism. Martmer, et. al., (2) in 1956 reported on the thyroid uptake of I-131 in 65 premature and 5 term infants varying in age from 1 to 63 days. The 24 hour thyroidal uptake following a 5 microcurie oral dose of iodine varied from 7 to 61 per cent. It was concluded that the activity of the thyroid in premature and full term infants was within the range considered normal for older children and adults.

In 1960 Ogborn, *et. al.*, (3) reported on the radioiodine uptake in the thyroid gland of 28 newborn infants from 3 to 7.5 days old. The infants received a 5 microcurie dose of I-131 via gastric tube. The 24 hour uptake varied from 6 to 36 per cent.

In 1962 Fisher *et al.*, (4) reporting on the results from 25 newborn infants, found that the mean 24 hour uptake following an intravenous dose of I-131 was 62 per cent with values ranging from 37 to 82 per cent. It was obvious from these conflicting reports that further work should be done in this area.

METHOD

Twenty-five newborn infants weighing between 5.5 and 8.5 pounds were chosen for this study, 13 of them were female, 12 were male. They all appeared

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[2]Supported in part by grants from AEC Biology and Medicine Division (AT(11-1)291) and American Cancer Society (T-159C.)

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to be normal, healthy infants. None of the mothers were under treatment for, nor gave a history of recent, thyroid disease. The studies were limited to infants less than 36 hours of age when the test was begun. The following parameters of thyroid function were measured:

1) serial determination of thyroidal I-131 uptake
2) cord blood erythrocyte uptake of I-131 labelled tri-iodothyronine
3) cord blood serum protein bound iodine
4) serum protein bound iodine of maternal blood taken at the time of delivery

Less than 1 microcurie of carrier free I-131 was administered to each infant by one of two methods: (1) Intramuscularly into the gluteus maximus; there were 17 in this group; (2) orally via a gastric tube, there were 8 in this group. At the time of injection an equal amount of I-131 solution was placed in a small rubber phantom closely resembling the shape and size of the normal infants thyroid. This was used as a standard.

The radio-activity in the thyroid gland was measured using a one inch NaI(T1) scintillation crystal. A 20° flat field collimator with a plastic spacer was used to maintain a constant target to crystal distance. The area covered was a circle of approximately 6 cm in diameter. Counting was done with the infants lying on their back with the neck hyperextended, and the plastic spacer touching the skin overlying the thyroid gland. Figure 1 shows the technique of obtaining

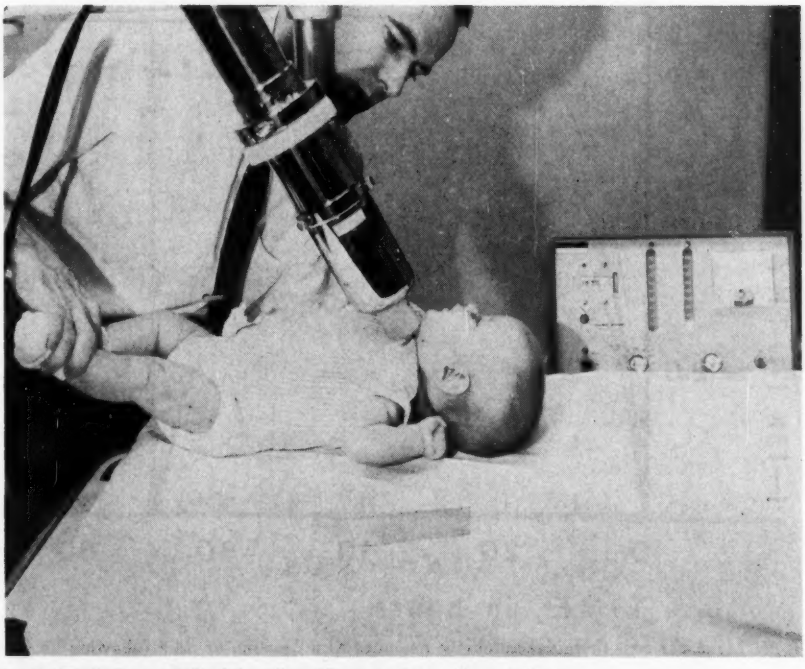

Fig. 1: Technique of obtaining thyroid counts in newborn infants.

the thyroid counts. A thigh count was subtracted from the neck count. This, divided by the background corrected standard count, was multiplied by 100 to give the per cent uptake. The infants were followed with serial uptakes from 2 to 8 hours apart for as long as they remained in the hospital, usually about 3 to 4 days.

The erythrocyte uptake of I-131 labelled tri-iodothyronine was done according to the method of Hamolsky (5). The protein bound iodine was determined by the wet ash method of Barker *et. al.* (6).

RESULTS

Figure 2 is a summary of the uptake studies for 17 infants receiving intramuscular radioiodine. The center solid line represents the arithmetical mean, the dotted lines represent the 95 per cent confidence limits. There was rapid concentration of radioiodine by the thyroid, reaching a maximum of about 70

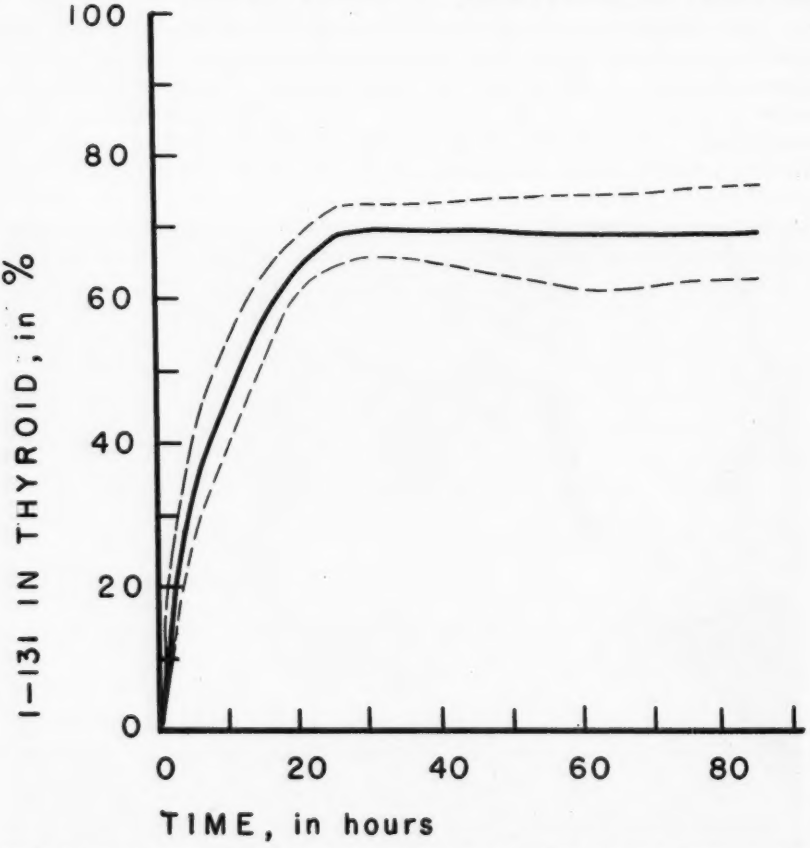

Fig. 2: Mean per cent thyroidal uptake in neonates as a function of time following an intramuscular injection of C. F. I-131. Dotted lines represent the 95 per cent confidence limits.

per cent at 25 hours. The 95 per cent confidence limits extended from about 65 per cent to 75 per cent at 25 hours. As compared to adult values, these are certainly abnormally high.

Figure 3 is a summary of the uptake studies for 8 infants receiving radioiodine orally. In comparison with Figure 2, two things are obvious. The first is that the rate of uptake is decreased such that the mean maximal uptake of about 50 per cent occurs at about 30 hours. There is much more variability of the data as is indicated by 95 per cent confidence limits at 30 hours extending from 35 to 60 per cent. These values of 45 per cent uptake at 25 hours and 50 per cent at 30 hours are at the upper limit and beyond those considered normal for adults.

The mean value of the maternal serum protein bound iodine was 9.8 ± 2.3 (S.D.)μg per cent. The mean value of serum protein bound iodine of cord blood was 8.6 ± 1.5 (S.D.) μg per cent. The mean value of the erythrocyte

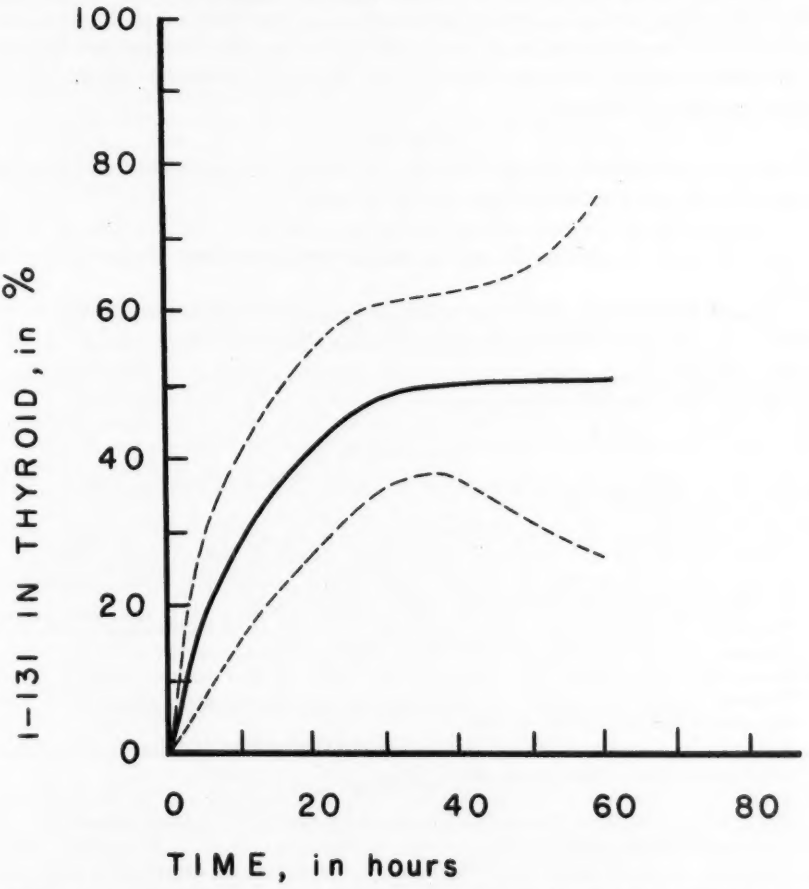

Fig. 3: Mean percent thyroidal uptake in neonates as a function of time following an oral dose of C. F. I-131. Dotted lines represent the 95 per cent confidence limits.

uptake of I-131 labelled tri-iodothyronine was 10.1 ± 1.3 (S.D.) per cent. These results are in approximate agreement with those of Spafford (7) and Danowski (8).

DISCUSSION

It is interesting to speculate as to the reason for these results. The extremely high uptake values for those infants receiving radioiodine intramuscularly may be explained on the basis of a physiologic hyperthyroidism. Turnover studies, of which we have done only a few, indicate that the biologic half life of iodine in the thyroid gland may be considerably shortened and of the order of 15 to 25 days, indicating a rapid turnover. On the other hand, the high uptake studies could be explained on the basis of an iodine starved gland, or a rapidly expanding thyroidal iodine pool. The functional status of the kidney in the newborn infant is also an important factor which should be evaluated.

Those children receiving radioiodine orally had uptake values considerably lower than those receiving it intramuscularly, and the time for peak concentration occurred some 5 or 6 hours later. The reason for this may be that there is a delayed absorption of iodide through the relatively immature mucosa of the infant gastrointestinal tract.

SUMMARY

Seventeen newborn infants receiving intramuscular radioiodine had a mean maximal thyroidal uptake of 70 per cent at 25 hours.

Eight newborn infants receiving oral radioiodine had a mean uptake of about 45 per cent at 25 hours and a mean maximum uptake of about 50 per cent at 30 hours.

The mean value of the maternal serum protein bound iodine was 9.8 ± 2.3 (S.D.) μg per cent. The mean value of serum protein bound iodine of cord blood was 8.6 ± 1.5 (S.D.) μg per cent. The mean value of the erythrocyte uptake of I-131 labelled triiodothyronine was 10.1 ± 1.3 (S.D.) per cent.

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CURRENT ABSTRACTS IN NUCLEAR MEDICINE

CARCINOMA OF THE THYROID GLAND IN CHILDREN AND ADOLESCENTS

NISHIYAMA, R. H., SCHMIDT, R. W. AND BATSAKIS, J. G.: *J.A.M.A.* 181:1034, Sept. 22, 1962

Thyroid cancer was treated and followed at the University of Michigan Medical Center in 36 children and adolescents during the last 30 years. The average time of diagnosis was 11.8 years (range 3-18). The average age at time of onset of clinical symptoms was 9.9 years.

Regional lymph node metastases were found in 32 (89%), while pulmonary metastases were present at time of diagnosis in 9 (25%). The pathologic diagnosis was mixed papillary and follicular in 72 per cent; pure papillary and pure follicular were found in 14 per cent each. Undifferentiated carcinoma was "conspicuous by its absence."

Treatment was variable. Total thyroidectomies were done on 28/36 and subtotal thyroidectomies on 5/26. Therapeutic doses of I^{131} were give to 29 patients postoperatively, and 8 of these had additional external irradiation.

Two patients died of the disease: both had widespread metastases, both were 3 years old and were the youngest in the group. Of the 7 others with pulmonary metastases treated with I^{131}, 6 have had complete resolution while one has remaining lesions which are stationary. Twenty-six patients are free of detectable neoplasm.

Of special interest is the fact that 17 (47%) of these patients had a history of therapeutic x-ray to the head and neck. The average time from therapy to histologic diagnosis of thyroid carcinoma was 8.8 years (range 5-12). Neither of the two patients who died had had previous irradiation. The authors comment on the apparent increase in incidence of thyroid carcinoma in children.

Abstracted by Robert A. Nordyke, M.D., Straub Clinic, Honolulu.

LOW SERUM PBI VALUES WITH CLINICAL EUTHYROIDISM IN I^{131} TREATED THYROTOXICOSIS

BURNETT, G. R., VAN BUREN, H. C. AND FALOON, W. W.: *J.A.M.A.* 181:1039, Sept. 22, 1962.

Seventy-eight patients with thyrotoxicosis were examined 1-7 years after treatment with II^{131} (29 had been previously treated surgically). Clinical judgment (low, normal, or high) was compared to the PBI (below 4 ugm%, 4-8, and over 8).

A considerable discrepancy between the two methods of evaluation was found. By clinical evaluation, 74.5 per cent were euthyroid, while only 46 per cent had normal PBI levels; 16.5 per cent were clinically hypothyroid, while 38.5 per cent had low PBI's; and 9.0 per cent were clinically hyperthyroid, while 15.5 per cent had elevated PBI's.

There appeared to be a lowering of the average PBI as the post-treatment years increased, but the significance of this finding is limited by the small number of patients involved.

Abstracted by Robert A. Nordyke, M.D., Straub Clinic, Honolulu.

IODINE-129: ITS OCCURRENCE IN NATURE AND ITS UTILITY AS A TRACER

R. R. EDWARDS, *Science* 137:851, 1962

Hardly a year passes without the addition of a new iodine isotope to the armamentarium of nuclear medicine. Each has its own particular advantages and disadvantages. This report summarizes the physical data concerning iodine-129 and outlines its potential advantages as a tracer. Edwards has not concerned himself with the biomedical uses of iodine-129, but these will be quite evident to anyone interested in thyroid physiology. In essence, I-129 is an isotope of iodine

that results from the fission of uranium. From the physical standpoint, it is radioactive, with a half-life of 1.6 x 10^7 years. From the biomedical standpoint, it is essentially stable because of its exceedingly slow rate of disintegration; its specific activity is 0.16 microcuries/milligram. How then can one use it as a tracer? Natural production rates from spontaneous fission and cosmic ray reactions yield a steady-state concentration of about 10^{-14} grams of I-129 per gram of I-127. For all practical purposes, I-129 is not present in the body. One can therefore determine iodine kinetics by following the rate of movement of I-129 administered through the metabolic cycle of iodine. How does one detect a nuclide with such a low specific activity? To do this, one utilizes the technique of neutron activation analysis, a procedure only recently introduced into the biomecial field. Instead of attempting to follow I-129 by measuring its intrinsic radioactivity, one subjects material or biological fluids containing I-129 to neutron bombardment. I-129 has a very high cross-section for capturing thermal neutrons and the resultant radionuclide, I-130, is readily detectable. If one uses a thermal neutron flux of 10^{14} n/cm ^{2}/sec., one increases the specific activity of I-129 by a factor of 2.3 x 16^6. An additional advantage is gained by the fact that the half-life of I-130 is 12.6 hours, thereby making it easy to separate from chlorine-38, the chief radiochemical contaminant in most biological material after neutron activation. Chlorine-38 has a half-life of 35 minutes and can therefore be separated by radioactive decay alone. Edwards summarizes the new vistas for I-129 as a tracer as follows: (1) the long half-life permits tracer studies of essentially infinite duration; (2) virtual elimination of the health hazard associated with the use of conventional radioactive tracers; (3) radiation effects on the system under study and on the labelled compounds are eliminated; (4) the radiotracer-activation method is superior to stable isotope tracing because the problem of reagent contamination is essentially absent.

This review strongly recommends the original article to everyone, but particularly to those interested in a new and exciting way to extend our knowledge of iodine metabolism.

Henry N. Wagner, Jr., M. D., Assistant Professor of Medicine, Div. of Nuclear Medicine, Johns Hopkins Medical Institutions, Baltimore

Announcement

The Second Special $1000 award of the American Nuclear Society will be given in June 1963 for work on "The Biological Effects of Radiation."

There are no standard forms for nominations, but nominators should spell out at length in a letter, all details on the person he is nominating, and discuss completely the nominee's contributions in the area of biological effects of radiation. The nominee need not be a member of the American Nuclear Society. Letters are to be sent, postmarked no later than April 1, 1963, to John W. Landis, Chairman, ANS Honors and Awards Committee, The Babcock & Wilcox Company, Kemper Street, Lynchburg, Virginia.

The award, consisting of $1000 and a citation, is given at the annual meeting of the American Nuclear Society to be held this year in Salt Lake City, June 17-19, 1963.

THE SOCIETY OF NUCLEAR MEDICINE

Tenth Annual Meeting

The Queen Elizabeth Hotel

Montreal, Canada

WEDNESDAY, JUNE 26, 1963

Morning Session

Registration—CONVENTION FOYER

9:00—Nominating Committee—GATINEAU ROOM

10:00—Joint Meeting of Board of Trustees and Executive Committee—ST. LAURENT ROOM

12:00—Executive Committee and Board of Trustees Luncheon—RICHELIEU ROOM

2:00—Joint Meeting of Board of Trustees and Executive Committee—ST. LAURENT ROOM

Evening Session

AUDITORIUM—UNIVERSITY OF MONTREAL

Co-Chairmen—J. R. MAXFIELD, JR., M.D., Dallas, Texas, President, Society of Nuclear Medicine

GEORGE J. STREAM, M.D., Montreal, Canada, President Northeastern Chapter, Society of Nuclear Medicine

MSGR. IRENE LUSSIER, Rector of the University of Montreal—Welcome on behalf of the University of Montreal.

HIS WORSHIP JEAN DRAPEAU, the Mayor of the City of Montreal—Welcome on behalf of the City of Montreal.

DR. H. ROCKE ROBERTSON, Principal and Vice Chancellor, McGill University Montreal.

DR. C. G. STEWART, Director, Medical Division, Atomic Energy of Canada Canadian contribution to the development of Nuclear Energy.

DR. JAMES R. MAXFIELD, JR., President of the Society of Nuclear Medicine.

DR. THAD SEARS, Denver, Colorado, President-Elect, Society of Nuclear Medicine.

PROFESSOR A. S. MACFARLANE, National Institute for Medical Research, Mill Hill London, England—Present lines of development of Nuclear Medicine in Britain and Europe.

DR. ROBERT MAASS E., Director, Nuclear Medicine Division, Mexican Nuclear Energy Commission, Mexico City—Present lines of development of Nuclear Medicine in Latin America.

LT. COLONEL DAVID E. LIVERMORE, United States Air Force Medical Corps, Washington, D.C.—The future of Nuclear Medicine and its relation to Space Medicine.

PROFESSOR JOSEPH STERNBERG, University of Montreal—The future of Nuclear Medicine in Public Health and Welfare.

DR. PAUL F. HAHN, United States Public Health Service, Washington, D.C.—Organization and support of research in Nuclear Medicine

THURSDAY, JUNE 27, 1963

Morning Session

8:30 A.M. Registration—CONVENTION FOYER

SESSION A

GRAND SALON

Chairman: FREDERICK J. BONTE, M.D., Dallas, Texas

9:00 A.M. Color Coded Digital Print-out for Radioisotope Scanning.
G. J. HINE, Boston. A 1.

9:15 A.M. Three Dimensional Scintiscanning.
L. M. LEVY and O. OKEZIE, Long Island. A 2.

9:30 A.M. Improvement of Quantum Utilization in Scanning or Other Methods of Distribution Visualization.
B. CASSEN and H. GASS, Los Angeles. A 3.

9:45 A.M. Scintillation Camera for *In Vivo* Studies of Dynamic Processes.
W. G. MYERS, Columbus. A 4.

10:00 A.M. Transmission of Radioisotope Scanner Intelligence.
B. KAWIN, S. FINGERHOOD and C. COPE, Fort Howard, Md. L. I., New York, Washington, D.C. A 5.

10:15 A.M. Some Important Considerations in the Use of Low-Energy Gamma Emitters in Scanning.
C. C. HARRIS, P. R. BELL, M. M. SETTERFIELD, and J. C. JORDAN, Oak Ridge. A 6.

10:30 A.M. Exhibit Break

SESSION B

JOLLIET AND MARQUETTE ROOMS

Chairman: IRVING M. ARIEL, M.D., New York City

9:00 A.M. Postoperative Treatment of Thyroid Cancer with Radioactive Iodine.
W. H. BLAHD, and J. M. KOPLOWITZ, Los Angeles. B. 1.

Letter and number following each title in the program refer to the corresponding abstract. The abstracts have been arranged by session and by order of presentation, and appear in the special convention issue of The Journal of Nuclear Medicine (May, 1963 issue).

9:15 A.M. The Management of Thyroid Carcinoma: The Place of Radioactive Iodine (I-131).
J. B. WORKMAN, Baltimore, Md. B 2.

9:30 A.M. Treatment of Equine Ocular Carcinoma with Cobalt-60 Implantation.
W. C. BANKS, College Station, Texas. B 3.

9:45 A.M. Blood Volume Determinations in Emergency Cases.
K. E. CORRIGAN and H. H. HAYDEN, Royal Oak, Michigan B 4.

10:00 A.M. Medical Application of Strontium-90 in Opthalmology.
I. A. ABOU SINNA, Cairo, UAR. B 5.

10:15 A.M. Exhibit Break.

THURSDAY, JUNE 27, 1963

Morning Session

8:30 A.M. Registration—CONVENTION FOYER

SESSION C

GRAND SALON

Chairman: H. C. ALLEN, JR., M.D., Houston, Texas

10:45 A.M. Comparison of Cerebral Angiograms Electroencephalograms and Radioisotope Cerebrograms in Evaluating Intracerebral Abnormalities.
D. E. JOHNSON, J. C. KENNADY, and G. V. TAPLIN, Los Angeles. C 1.

11:00 A.M. Localization of Brain Tumor with I-131 Labeled Polyvinylprrolidone.
W. N. TAUXE, P. J. PITLYK, R. E. SEDLACK, F. W. KERR and H. J. SVIEN, Rochester. C 2.

11:15 A.M. The Results of 350 Brain Scans with Radioactive Mercurial Diuretics.
D. B. SODEE, Washington, D.C. C 3.

11:30 A.M. Scintillation Scanning of the Kidneys with Neohydrin-Mercury-203.
F. J. BONTE, F. W. RILEY, V. V. KIRBY and T. D. ALLEN, Dallas. C 4.

11:45 A.M. The Evaluation of Renal and Cardiac Dynamics with the Autofluoroscope.
M. A. BENDER and M. BLAU, Buffalo. C 5.

SESSION D

JOLLIET AND MARQUETTE ROOMS

Chairman: JOHN H. LAWRENCE, M.D., Berkeley, California

10:30 A.M. Therapeutic Intralymphatic Infusion of Radioactive Isotopes.
I. M. ARIEL, M. RESNICK, and D. GALEY, New York. D 1.

10:45 A.M. The Therapeutic Use of Radioactive Gold Seeds in Neoplasms.
P. LACHANCE and A. F. VALLEE, Montreal, Canada. D 2.

11:00 A.M. Properties and Medical Uses of Radioactive Ceramic Microspheres.
T. N. LAHR, C. J. HALVA, and J. P. RYAN, St. Paul, Minn. D 3.

11:15 A.M. Intragastric Irradiation with Ru-Rh^{106}; Results with Fractional Dosage in Patients with Peptic Ulcerative Disease and with Gastric Neoplasms.
R. C. FRUIN, M. LITTMAN and A. LITTMAN, Chicago. D 4.

11:30 A.M. Internally Administered Y-90 DTPA in Preparation for Homografting of Tissues in Dogs and Man.
H. S. WINCHELL, M. POLLYCOVE, W. D. LOUGHMAN, and J. H. LAWRENCE, San Francisco. D 5.

11:45 A.M. Intralymphatic Administration of Radioisotopes to Lymph Nodes.
T. HONDA, J. J. RAFTER and G. C. KYLER, Oak Ridge. D 6.

THURSDAY, JUNE 27, 1963

Afternoon Session

SESSION E

GRAND SALON

Chairman: MERRILL A. BENDER, M.D., Buffalo, New York

1:30 P.M. A Comparison of the Distribution of Au-198, I-131 Rose Bengal and Mo-99 in Normal and Abnormal Liver Tissue in Rats.
C. T. KNORPP, L. COUSINEAU, M. H. RENNIE and J. MANNARD, Ann Arbor, Mich. E 1.

1:45 P.M. Improved Liver Scanning with 6-Hour Tc^{99m} in Fat Emulsion.
P. V. HARPER, K. A. LATHROP and R. J. MCCARDLE, Chicago. E 2.

2:00 P.M. The Comparison of Colloidal Gold-198 and Colloidal Gold-199 for Liver Scanning.
J. H. CHRISTIE and W. J. MACINTYRE, Cleveland. E 3.

2:15 P.M. Radioisotope Photoscanning and Hemodynamic Pattern of the Liver in Hepato-Splenic Schistosomiasis.
M. A. RAZZAK, Cairo, Egypt. E 4.

2:30 P.M. The Use of Hg-203 Labelled Bromomercurihydroxypropane (BMHP) in Radioactive Scanning of the Spleen.
H. N. WAGNER, J. G. MCAFEE, I. M. WEINER, M. IIO, J. MARTINEZ and W. P. CAINE, Baltimore, E 5.

2:45 P.M. Renal Uptakes and Renal Scanning with Radioactive Mercury^{197} Neohydrin and Mercury^{203} Neohydrin.
D. B. SODEE, Washington, D.C. E 6.

3:00 P.M. Exhibit Break

THURSDAY, JUNE 27, 1963

Afternoon Session

SESSION F

JOLLIET AND MARQUETTE ROOMS

Chairman: H. L. JAFFE, M.D., Los Angeles, California

1:30 P.M. The Response of Disseminated Reticulum Cell Sarcoma to the Intravenous Injection of Colloidal Radioactive Gold.
P. RUBIN and S. H. LEVITT, Rochester, New York. F 1.

1:45 P.M. Triiodothyroidism—Clinical Problems.
P. CZERNIAK and S. CHAITCHIK, Tel-Hashomer, Israel. F 2.

2:00 P.M. Determination of Protein-Bound Iodine (PBI) in Human Plasma by Thermal Neutron Activation Analysis.
E. M. SMITH, J. M. MOZLEY, H. N. WAGNER, and R. REBA, Baltimore, Md. F 3.

2:15 P.M. A Clinical Comparison of a Test of Thyro-Binding with the Standard PBI.
J. F. SCHOLER, Palto Alto, California. F 4.

2:30 P.M. The Resin Sponge Modification of the T-3 Test.
G. B. MCADAMS and R. F. REINFRANK, Hartford, Conn. F 5.

2:45 P.M. Exhibit Break

SESSION G

GRAND SALON

Chairman: H. WAGNER, M.D., Baltimore, Maryland

3:15 P.M. Gastric Photoscans with Colloidal Aggregates of Radioalbumin (Mechanism, Diagnostic and Therapeutic Implications).
G. V. TAPLIN, D. E. JOHNSON, E. K. DORE, H. S. KAPLAN, Torrance, Calif. G 1.

3:30 P.M. Diagnosis of Pancreatic Disease by Photoscanning.
T. P. HAYNIE, A. C. SVOBODA, and G. D. ZUIDEMA, Ann Arbor, Michigan. G 2.

3:45 P.M. Clinical Experience with F-18 and Sr-87m for Bone Scanning.
M. Blau, Y. Laor, and M. A. Bender, Buffalo, New York. G 3.

4:00 P.M. Early Diagnosis of Metastatic Bone Cancer by Photoscanning with Strontium-85.
N. D. Charkes and D. M. Sklaroff, Philadelphia. G 4.

4:15 P.M. Kinetic Studies of Calcium Based on Saliva and Total Body Retention Measurements of Sr^{85} and Ca^{47}.
E. Greenberg, M. Merlino, D. Weber, K. R. Corey, P. Kenny, and J. S. Laughlin, New York. G 5.

4:30 P.M. Localization of Eye Tumors by External Counting Utilizing Mercury ^{203} Neohydrin.
D. B. Sodee, Washington, D.C. G 6.

4:45 P.M. Quantitative Comparison of RISA and Radio-Mercury in Brain Scanning.
W. Feindel, L. Yamamoto, and N. Rumin, Montreal, Canada. G 7.

SESSION H

JOLLIET AND MARQUETTE ROOMS

Chairman: Lindon Seed, M.D., Chicago, Illinois

3:00 P.M. Studies on 24-Hour PBI—I-131 Conversion Ratios by an Ultrafiltration Technique.
A. Miale, P., J. S. Burkle, P. M. Dettman, and T. Talley, Bethesda, Maryland. H 1.

3:15 P.M. A Metabolic Defect Associated with Exophthalmos and Thyroid Disease.
P. C. Johnson, T. R. Redding, L. Wade and J. Jona, Houston, Texas. H 2.

3:30 P.M. Evaluation of Potassium Iodide as a Thyroid Suppressive Agent and Its Comparison with Triiodothyronine (Cytomel).
M. Spring, O. Gallego and L. Jones, Bronx, New York. H 3.

3:45 P.M. The Use of Radioisotopes in the Diagnosis of Hyperthyroidism in Infants.
C. Imperato, Parma, Italy. H 4.

4:00 P.M. An Approach to the Definition of Preclinical Disease.
N. Naumoff, Detroit, Michigan. H 5.

4:15 P.M. Analog Computer Simulation of Radioiodine Tracer Studies in Thyroid Disease.
D. W. Brown and A. L. Kretchmar, Oak Ridge. H 6.

4:30 P.M. Studies in Radiomicrobiology: Distribution of I^{131}-labeled Staphylococcal Enterotoxin in Young Cat.
C. Arghittu, L. Lenzerini and M. Rossi-Torelli, Grado, Pisa, Italy. H 7.

4:45 P.M. Studies on the Radiobiological Effects of Thymidine-H-3 During its Incorporation Into the DNA of Landschutz Ascites Tumor Cell.
J. Cross, Jerusalem, Israel. H 8.

EVENING SOCIAL HOUR AND ANNUAL BANQUET

GRAND SALON

6:45— 7:45 Social Hour—Cocktails (Courtesy of Technical Exhibitors)
8:00— 9:00 Annual Banquet (Dress Optional)
9:30—12:00 Dancing

FRIDAY, JUNE 28, 1963

Morning Session

8:30—Registration—CONVENTION FOYER.

SESSION J

GRAND SALON

Chairman: CHARLES HLAD, M.S., Ft. Logan, Colorado

9:00 A.M. Potassium Changes in the Cardiac Muscle as Studied by a K^{40} Method.
P. CZERNIAK and I. KARIV, Tel-Hashomer, Israel. J. 1.

9:15 A.M. The Use of Instrumentation to Subtract Blood Pool From Parenchymal Radioactivity for Determining the Hepatic Uptake of I-131 labeled fat.
J. R. MCLAREN, W. B. MILLER and W. D. DREW, Atlanta, Ga. J 2.

9:30 A.M. The Development of a New Diagnostic Test for Liver Function Using Radioiodinated Benzoic Acids.
M. TUBIS, W. H. BLAHD, J. S. ENDOW, and S. S. RAWALAY, Los Angeles, California. J 3.

9:45 A.M. The Distribution of Rb^{86} in the Dog's Heart.
B. MALAMOS, S. MOULOPOULOS, P. KOSTAMIS, E. PARASCHOU, and K. ILIAS, Athens, Greece. J 4.

10:00 A.M. Whole Body Iron Loss Measured with a Gamma Spectrometer.
H. SAITO, T. W. SARGENT, H. G. PARKER and J. H. LAWRENCE, Berkeley, Calif. J 5.

10:15 A.M. Distribution of $Iron^{59}$ in the Rat Following Gastric Administration of Labeled Ferrocene.
A. F. DRATZ, J. C. COBERLY and J. H. GOLESTEIN, Atlanta, Ga. J 6.

10:30 A.M. Exhibit Break

FRIDAY, JUNE 28, 1963

Morning Session

8:30—Registration—CONVENTION FOYER

SESSION K

JOLLIET AND MARQUETTE ROOMS

Chairman: ERVIN KAPLAN, M.D., Hines, Illinois

9:00 A.M. The Uptake of Radioactive Cesium and Rubidium by Normal and Infarcted Myocardium.
E. A. CARR, Ann Arbor, Michigan. K 1.

9:15 A.M. Coronary Circulation Studies with Rubidium-86.
L. DONATO, Pisa, Italy. K 2.

9:30 A.M. An Approach to the Scanning of Pulmonary Infarcts.
J. L. QUINN, III., J. E. WHITLEY and S. A. HUDSPETH and F. C. WATTS, Winston-Salem, North Carolina. K 3.

9:45 A.M. Measurement of Pericardial Fluid Correlated with the I-131 Cholografin(R) Heart Scan.
D. M. SKLAROFF and N. D. CHARKES, Philadelphia. K 4.

10:00 A.M. Factors which Activate the Coronary Collateral Circulation. A Study with Radioactive Beads.
H. L. JAFFE, E. CORDAY, H. ALPERN, R. BLUM and M. MEREDITH, Los Angeles. K 5.

10:15 A.M. Exhibit Break

SESSION L

GRAND SALON

Chairman: THAD SEARS, M.D., Denver, Colorado

10:45 A.M. The Retention of Strontium-85 in Healthy and Diseased Bones of Patients with Breast Cancer.
K. R. COREY, E. GREENBERG, D. WEBER, P. KENNY, and J. S. LAUGHLIN, New York. L 1.

11:00 A.M. Intestinal Transport of Radiolabeled Vitamins.
R. P. SPENCER and T. M. BOW, Buffalo, New York. L 2.

11:15 A.M. Radiostrontium-87m in Studies of Healing Bone Fracture.
W. G. MYERS and M. OLEJAR, Columbus, Ohio. L 3.

11:30 A.M. Retention of Radioisotopes by Hair, Bone and Vascular Tissues.
W. H. STRAIN, W. P. BERLINER, C. A. LANKAU, R. K. MCEVOY, W. J. PORIES and R. H. GREENLAW, Lexington, Ky. L 4.

11:45 A.M. Selective Isotopic Labeling of the Parathyroid Gland.
E. J. POTCHEN, Boston. L 5.

SESSION M

JOLLIET AND MARQUETTE ROOMS

Chairman: JACK S. KROHMER, M.S., Dallas, Texas

10:30 A.M. The Uptake of I-131 Labeled Aminoacridine Compounds by Lung Tumors in Rats.
N. B. ACKERMAN, Minneapolis, Minn. M 1.

10:45 A.M. Chromatographic Determination of Inorganic 'Unbound' Iodide (I-131 and I-125) in Various Radioiodinated Pharmaceuticals.
N. S. STERN and H. HULIT, New Brunswick, N. J. M 2.

11:00 A.M. In-Vivo Radiophotoluminescent Dosimetry.
C. G. AMATO, S. J. MALSKY, B. ROSWIT and B. REID, Bronx, N. Y. M 3.

11:15 A.M. A Study of Thermoluminescent Dosimetry.
S. J. MALSKY, C. G. AMATO, B. ROSWIT and C. SPRECKELS, Bronx, New York, M 4.

11:30 A.M. Autoradiographic Demonstration of Thorium Deposition in Tissues.
H. LANZ, and S. KELLER, Dallas. M 5.

11:45 A.M. Neutron Penetrations in a Phantom Head.
R. G. FAIRCHILD, Upton, L. I., New York. M 6.

FRIDAY, JUNE 28, 1963

Afternoon Session

SESSION N

GRAND SALON

Chairman: J. R. MAXFIELD, M.D., Dallas, Texas

1:30 P.M. Pituitary Elimination by Radioactive Implants in Patients with Mammary and Prostatic Carcinoma.
K. SCHEER, Heidelberg, Germany. N 1.

1:45 P.M. The Proton and Alpha Particle Beam and the Bragg Curve in Medicine.
J. LAWRENCE, C. TOBIAS, J. BORN, L. LINFOOT, A. GOTTSCHALK, and R. KLING, Berkeley, California. N 2.

2:00 P.M. Clinical Use of Radiocopper (for Early Diagnosis of Wilson's Disease and Schizofrenia).
P. CZERNIAK, Tel-Hashomer, Israel. N 3.

2:15 P.M. Use of P-32 and a Miniature Geiger Tube to Detect Malignant Neoplasia of the Gastrointestinal Tract.
R. NELSON, W. DEWEY and R. ROSE, Houston, Texas. N 4.

2:30 P.M. Business Meeting

3:15 P.M. Intermission

3:40 P.M. FOURTH ANNUAL NUCLEAR PIONEER LECTURE IN HONOR OF PROFESSOR ENRICO FERMI (1901-1954).

Presiding: J. R. MAXFIELD, JR., M.D., Dallas, Texas, President Society of Nuclear Medicine

Guest Lecturer and Recipient of FOURTH ANNUAL NUCLEAR PIONEER LECTURE SCROLL: Professor Emilio Segrè University of California

Presentation of Scroll: John U. Hidalgo, M.S., New Orleans, Louisiana, Chairman, 1963 Program Committee

SATURDAY, JUNE 29, 1963

Morning Session

8:30 Registration—CONVENTION FOYER

SESSION O

DULUTH AND MACKENZIE ROOMS

Chairman: R. NORDYKE, M.D., Honolulu, Hawaii

9:00 A.M. The Pulmonary Circulation Time and Radiocariographic Pattern in Bilharzial Cor Pulmonale.
M. A. RAZZAK, Cairo, Egypt. O 1.

9:15 A.M. Red Cell Survival in Primary and Metastatic Cancer.
K. BAUER, J. WALKER and J. LESTINA, Los Angeles. O 2.

9:30 A.M. The Simultaneous Use of Fe-59, Cr-51 and Co-57 in the Study of the Erythrokinetics of the Postgastrectomy State.
D. R. SANTSCHI, W. N. TAUXE, and H. H. SCUDAMORE, Rochester, Minn. O 3.

9:45 A.M. Lanthanum-140 as a measure of the Completeness of Stool Collections for the Oral Iron-59 Absorption Test.
R. L. HAYES, B. NELSON and J. E. CARLTON, Oak Ridge. O 4.

10:00 A.M. Total Iron-Binding Capacity in Normal Pregnancy.
G. D. MALKASIAN, W. N. TAUXE, A. B. HAGEDORN, Rochester, Minn. O 5.

10:15 A.M. Physiological Effects on Erythrocytic Factors in Dogs. Part I. Effect on Blood Volumes and Red Blood Cell Regeneration.
M. BERG, Garfield Heights, Ohio. O 6.

10:30 A.M. Exhibit Break

SATURDAY, JUNE 29, 1963

Morning Session

8:30—Registration—CONVENTION FOYER

SESSION P

GRAND SALON

Chairman: R. KNISELEY, M.D., Oak Ridge, Tenn.

9:00 A.M. Individual Renal Plasma Flow (Quantitative Methods with Radiohippuran).
E. K. DORE, G. V. TAPLIN, D. E. JOHNSON and H. S. KAPLAN, Torrance, Calif. P 1.

9:15 A.M. Principles of Rates in Relation to the Renogram and Thyroid Uptake.
S. TAPLITS, Cincinnati, Ohio. P 2.

9:30 A.M. Detection of Unilateral Renal Disease by Measurement of the Rate of Uptake of Hg-203 Chlormerodrin.
R. REBA, J. MCAFEE and H. WAGNER, Baltimore, Maryland. P 3.

9:45 A.M. The Value of the Renogram in Following Patients through Pelvic or Abdominal Irradiation.
J. GREEN, R. BRUNEAU, and P. RUBIN, Rochester, New York. P 4.

10:00 A.M. Renograms and Cardiac Studies with a Single Probe.
D. L. TABERN and L. HALPERIN, Highland Park, Illinois. P 5.

10:15 A.M. A Diagnostic Score Useful for Evaluating the Renogram of Hypertensive Patients.
P. C. JOHNSON and D. D. ODOM, Houston, Texas. P. 6.

10:30 A.M. Experience with Determination of Blood Volume in a General Hospital.
M. IHNEN and D. KELSEY, Augusta, Ga. P 7.

10:45 A.M. Exhibit Break

SESSION Q

DULUTH AND MACKENZIE ROOMS

Chairman: R. MURRAY CUNNINGHAM, M.D., Montreal, P.Q.

10:45 A.M. A Clinical Test Useful in the Determination of Portal Hypertension.
R. EICHHORN, S. SIMKIN and P. C. JOHNSON, Houston, Texas. Q 1.

11:00 A.M. Measurement of Forearm Blood Flow in Man with Radioactive Krypton and Xenon.
G. HOLZMAN, H. WAGNER, M. IIO, D. RABINOWITZ, and K. ZIERLER, Baltimore, Md. Q 2.

11:15 A.M. Radioactive Krypton and Xenon in the Measurement of Coronary Hepatic and Cerebral Blood Flow.
M. IIO, H. WAGNER, R. ROSS, K. UEDA, P. LICHTLEN, J. JUDE, G. KNICKERBOCKER and H. BOURNE, Baltimore, Maryland. Q 3.

11:30 A.M. Clinical Measurement of Brain Permeability to Gamma-emitting Labeled Compounds.
W. Oldendorf and M. Kitano, Los Angeles, California. Q 4.

11:45 A.M. The Elasticity of the Cranial Blood Pool.
M. Kitano and W. Oldendorf, Los Angeles, California. Q 5.

12:00 A.M. Observations of Cerebral Arterio-venous Transit Time Using Radio Iodinated Human Serum Albumin.
R. Bell, Wadworth, Kansas. Q 6.

12:15 P.M. Sr-90 Metabolism in Man During Low Sr-90 Intake.
H. Spencer and J. Samachson, E. Hardy, and J. Rivera, Hines, Illinois and New York. Q 7.

12:30 P.M. A Study of the Uptake of T-3 by Dry Resin.
W. Diguilio, P. Weinhold and G. Thoma, St. Louis, Mo. Q 8.

12:45 P.M. Screening of Unselected Hypertensive Patients with Radiorenography.
R. A. Nordyke and A. M. Brault, Honolulu, Hawaii. Q 9.

SESSION R

GRAND SALON

Chairman: R. Lackey, M.D., Denver, Colorado

11:00 A.M. C^{14} Tripalmitin Disappearance Curves in the Human.
L. Feinberg, H. Sandberg, L. Semana, S. Bellet, A. Ruttenberg, and S. Milke, Philadelphia, Pa. R 1.

11:15 A.M. Metabolic Fate of I-131 Antipyrine.
E. Gabrieli, T. Pyzikiewicz, Buffalo and M. A. Sullivan, New York R 2.

11:30 A.M. Studies of Tooth Movement Using Calcium-45 in Dogs.
A. Juda, J. Sklaroff, D. Cohen and J. Rabinowitz, Philadelphia. R 3.

11:45 A.M. Use of Radioactive Vitamin B^{12} to Measure the Glomerular Filtration Rate (GFR).
W. Nelp and H. Wagner, Seattle, Washington and Baltimore, Md. R 4.

12:00 A.M. Cr-51 Albumin Studies of Gastro-Intestinal Protein Loss in Patients with Malabsorbtive Disorders.
M. Croll and D. Berkowitz, Philadelphia. R 5.

12:15 P.M. The Competitive Effect of Varying Particles Sizes on the Clearance of Colloidal Material by the Reticuloendothelial System.
R. Schapiro and W. MacIntyre, Cleveland, Ohio. R 6.

12:30 P.M. Direct Assay of Co-60 in Large Volumes of Urine.
R. Veatch, C. Decker, B. Kotlowski and E. Kaplan, Hines, Illinois. R 7.

A 1. *"Color Coded Digital Print-out for Radioisotope Scanning."* GERALD J. HINE (Radioisotope Service, Veterans Administration Hospital, Boston.)

Quantitative information can be obtained from a scan if the color of the print-out changes with the count-rate. The printing pattern shows then the radioisotope distribution and the printing color serves as a code for a digital evaluation of the scan. This delineates clearly areas with small differences in count-rate, between 10 to 15 per cent, without losing any information due to a preselected cut-off level.

For the color printing 8 parallel colored typewriter ribbons are employed. They are mounted on rolls on both sides of a carriage with a slit at the center where the printing stylus hits the ribbons. The carriage moves the ribbons back and forth beneath the tapper close to the paper. The movement of the carriage is controlled by a count-rate meter with a time constant of 0.3 sec. The output of the count-rate meter is connected to the servomechanism of a stripchart recorder which moves the carriage so that the tapper strikes a particular ribbon selected by the count-rate.

The operation of the color-scan requires finding the approximate maximum count-rate and the selection of a scale factor for the printing. After completion of the scan the results are immediately available in their final form without further processing. This color coded print-out method is simple and reliable and yields a maximum amount of information in a form which can be easily interpreted.

A 2. *"Three-Dimensional Scintiscanning."* LESTER M. LEVY, and OKOGBUE OKEZIE. (Division of Nuclear Medicine, Long Island Jewish Hospital, Long Island.)

The subjects of most medical scintiscanning are generally solid and three-dimensional but current scanning procedures produce a two-dimensional planar representation leading to considerable loss of information.

A successful technic of obtaining three-dimensional or stereo scintiscanning has been developed and the results obtained in both phantoms and patients point up the extra information now achievable.

In phantoms, it has been possible to stereoscan multiple sources at different levels or planes and to view the resulting stereoscan and achieve a near perfect representation of the original arrangement, in a single stereo picture.

In patients, stereoscans have revealed details of thyroid gland structure invisible on the conventional scintiscans. It has been possible to ascertain that palpable nodules are themselves active and not "cold" nodules superimposed upon normal thyroid tissue behind. In some cases, nodules have become visible only on the stereoscans as the technic separates the nodule activity from that behind.

Stereoslides of the stereoscans will be presented as examples of the approach which to date has utilized our conventional scanning equipment. It is hoped, however, that it will be possible to create a stereoscanner which will permit stereoscanning in one operation and thusly extend the technic to other areas now limited by the time required.

A 3. *"Improvement of Quantum Utilization in Scanning or Other Methods of Distribution Visualization."* BENEDICT CASSEN, and HERBERT GASS (Laboratory of Nuclear Medicine and Radiation Biology, University of California, Los Angeles.)

A careful analysis of the factors determining the quality, resolution, run time, dose requirements, etc., of scanning or other methods of radioisotope distribution determination, show that several, or all of these factors can be markedly improved by increased utilization of the gamma quanta emitted from a resolution element of activity. Efforts have been made in

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**Letter and number following each title in the Program refer to the corresponding abstract. The abstracts have been arranged by session and by order of presentation, and appear in the special convention issue of* The Journal of Nuclear Medicine (May, 1963 issue).

this direction by the original development of the converging collimator at Oak Ridge, the Anger camera and even more so in the so-called autofluoroscope of Bender. If mechanical scanning can be done fast enough, it can attain the same information gathering ability as the more complex and expensive electronic exhibiting methods. To test out the possibilities of a system of scanning with greatly improved quantrum utilization, a 2,000 hole converging collimator was constructed in the form of a spherical cap. This cap subtends a solid angle of almost pi-square radians to a resolution element of activity and as the collimator cap is 11½ inches in diameter on the smaller radius end and 15 inches on the larger end, it would be a major undertaking of considerable cost to use an approximately 20-inch diameter crystal as the detector. As no accurate pulse height resolution is needed, the detector problem was solved with use of a two-inch thick multicrystal layer in the form of a spherical cap. This layer is looked at by seven two-inch photomultiplier tubes.

The details of construction and performance of this scanner will be presented. This development program is supported by the Division of Biology and Medicine of the Atomic Energy Commission.

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A 4. *"Scintillation Camera for In Vitro Studies of Dynamic Processes."* William G. Myers (Department of Medicine, Physiology, and Radiology, The Ohio State University Health Center, Columbus.)

The scintillation camera, invented several years ago by Hal Anger, uniquely provides the opportunity to demonstrate *in vivo* the dynamicity of some biological processes. This ingenious instrument displays projections of accumulations of ions and compounds labeled with γ-isotopes to form pictures that reveal the relative spatial concentrations of them.

A principal advantage of the scintillation camera is that point-by-point scanning occurs electronically, in contrast with the familiar conventional mechanical line scanning. Moreover, the system for achieving directionality remains stationary. The entire area of interest is examined during the scanning period, and this is advantageous statistically. These features combine to enable one to take a series of pictures in very rapid sequence.

The advent of a commercial version of the scintillation camera is making studies in this laboratory readily feasible that had proved not to be practicable by means of our mechanical scanning machine. Sequential pictures are being made of rapidly changing distributions in time of γ-labeled compounds which have short biological or physical half times.

The scintillation camera is proving to be especially useful in experimental "atomic pharmacology" in studies of the relative rates of migration of compounds labeled with γ-isotopes into organs after different routes of administration. The screening of these "γ-ray carrier" compounds for selection for potential applications in Nuclear Medicine is thereby greatly facilitated.

A 5. *"Transmission of Radioisotope Scanner Intelligence."* Bergene Kawin, Stanford Fingerhood, and Clyde B. Cope (Radioisotope Service, Veterans Administration Hospital, Fort Howard, Maryland; Digitronics Corporation, Albertson, Long Island; and Veterans Administration, Washington.)

This paper describes an improved system for the interpretation of radioisotope scanner data. The systems configuration consists of four major sections, consisting of (1) Recording Station, (2) Bi-directional transmission system, (3) Computer Processor, and (4) Display Print-out Device. The recording station records the data from a standard radioisotope scanning head onto punched paper tape. The bi-directional transmission system transmits the data in punched tape and simultaneously converts it to magnetic tape for direct entry into the computer for analysis. The computer processor is an IBM 7094 and the computer program is a contour map generator written in SOS language. The computer output is magnetic tape which is transmitted back to the originating point via the bi-directional transmission system, where it is punched out on paper tape. The punched paper tape is then fed into the printout device which produces the contour map. The system increases accuracy and reduces prob-

lems of definition and distortion. By permitting display of data remotely, options are provided for (1) multiple scanner usage of a single data center, and (2) multiple interpretation and diagnosis.

A 6. *"Some Important Considerations in the Use of Low-Energy Gamma Emitters in Scanning."* C. C. HARRIS, P. B. BELL, M. M. SETTERFIELD, and J. C. JORDAN (Oak Ridge National Laboratory, Oak Ridge.)

It has been stated that collimator isoresponse plots obtained in air are invalid for sources *in vivo* or in water, because attenuation shifts the "focus" region toward the collimator, thus "shallowing" the response. We have believed that at most gamma ray energies encountered in scanning, this shift is unimportant. We also believe that, while patient attenuation tends to emphasize proximal activity, the sharpest scanning image occurs with the target at the "air focal distance."

Calculations on existing isoresponse data confirm that, though attenuation decreases the counting rate from a source in water compared with the same source in air, there are no marked alterations of the isoresponse plots at energies above around 140 kev. The same is true in the region from 60 to 140 kev when only gamma rays at the emitted energy are considered, but scattering effects are cause for concern.

Experimental scans made with I-131, Co-57, HG-197 and I-125 show that use of the "air focal distance" for maximum sharpness is proper even when the source is *in vivo*. They also show the smearing effect of scattering when the gamma ray energy is such that scattered rays emerge at such energies that they will be included in a spectrometer window set for the total absorption peak (Hg-197).

B 1. *"Postoperative Treatment of Thyroid Cancer with Radioactive Iodine."* WILLIAM H. BLAHD and JERRY M. KOPLOWITZ (Radioisotope Service, Veterans Administration Center, Los Angeles.)

The present report is a review of our experience since 1949 in the postoperative treatment of thyroid cancer with I^{131}. Forty-five patients have received therapeutic amounts of I^{131} and 43 have been followed for more than one year. Cancer metastases and postsurgical remnants were localized by means of the mechanical scintiscanner after patients had received large tracer doses of I^{131} preceded by injections of thyrotropic hormone. I^{131} uptake was demonstrable in the lesions of two-thirds of the patients with cancer metastases. Individual therapeutic doses of I^{131} averaging 100 millicuries, preceded by thyrotropic hormone injections, were administered to patients with functioning metastases. Smaller doses were employed to ablate postsurgical thyroid remnants. All patients received thyroid extract in tolerance doses upon the completion of I^{131} therapy. Tumors were differentiated cell types with the exception of two undifferentiated and two Hurthle cell carcinomas. No complications from I^{131} therapy were observed in the present series. This is attributed both to the conservative therapy dosage regimen employed and to the complete excision of normal thyroid and tumor tissue whenever possible.

B 2. *"The Management of Thyroid Carcinoma: The Place of Radioactive Iodine (I-131)."* JOSEPH B. WORKMAN (University of Maryland School of Medicine and University Hospital, Baltimore.)

Radioactive Iodine (I-131) has been a major factor in the successful management of 100 patients with proven thyroid carcinoma seen at the University of Maryland School of Medicine during the period 1951-1962. A total of 150 pathologically proven cases of thyroid malignancy were seen in this 11 year period and the decision to use radio-iodine therapy was based, in part, on the following criteria: 1) scintigram evidence of functioning thyroid tissue showing I-131 avidity following previous surgical thyroidectomy for thyroid cancer. 2) scintigram evidence of local or distant metastases demonstrating I-131 avidity following prior thyroidectomy and administration of thyroid stimulating hormone (TSH). In no instance was radio-iodine therapy alone utilized without prior surgical removal of all possible thyroid tissue.

The period of followup of these 150 patients extends from 1 to 11 years. In view of this relatively short period, no categorical statement can be made regarding "cure" rates. Response to therapy has been correlated with site of disease, age at diagnosis, and tumor histology of both primary tumor and where feasible, metastases. The application of radioisotope scintillation scanning to the better management of thyroid cancer, is demonstrated. The need for prompt recognition and complete surgical and radio-iodine therapy is most important to the eventual satisfactory management of this uncommon but malignant disease.

B 3. *"Treatment of Equine Ocular Carcinoma with Cobalt 60 Implantation."* W. C. Banks (School of Veterinary Medicine, Agriculture and Mechanical College of Texas, College Station.)

The paper includes a brief discussion of the incidence and probable causes for the condition. Attention is called to the much higher incidence of animals with non-pigmented skin around the eye.

Slides will be shown that demonstrate the types of carcinomas seen in several species of farm animals, the technique of implantation is demonstrated, and the results of the Cobalt 60 therapy indicated. Up to the present time, about 100 animals have been treated for carcinoma with this mode of therapy in the past 8 years.

B 4. *"Blood Volume Determinations in Emergency Cases."* K. E. Corrigan, and H. H. Hayden (William Beaumont Hospital, Royal Oak, Michigan.)

During the past six years (to April 1, 1963) 2206 blood volume determinations have been performed on 1259 patients at William Beaumont Hospital. Most of these have been emergency situations involving: (1) acute accidental injuries, (2) gastric bleeders, (3) surgical emergencies, and (4) obstetrical hemorrhage. The number of determinations per patient has ranged from one to seven in any one sequence. Some of the patients have had repeated admissions at intervals of one year or more. The technical procedure, accuracy, and repeatability of the results, and application in difficult problems, particularly occult abdominal bleeding and major fractures are illustrated.

B 5. *"Medical Application of Strontium-90 in Ophthalmology."* Ibrahim A. Abou Sinna (Cairo)

The general principles, physical and biological properties of beta irradiation from a strontium 90 applicator are discussed. This applicator is a useful source or radiation which has been effective in the control of various eye lesions such as vascularization, pterygia, vernal catarrh; tumors of the eye and conjunctiva, infections and inflammatory conditions.

A summary of the results of treatment of 183 cases treated in private practice over a period of seven years is given including the method of treatment and range of dosage.

The value of treatment of trachomatous complications is pointed out.

C 1. *"Comparison of Cerebral Angiograms, Electroencephalograms and Radioisotope Cerebrograms in Evaluating Intracerebral Abnormalities,"* DeLores E. Johnson, John C. Kennady, and George V. Taplin (Nuclear Medicine Division, Department of Radiology and Department of Neurosurgery, Los Angeles County Harbor General Hospital, Torrance; Laboratory of Nuclear Medicine and Radiation Biology, UCLA Medical School, Los Angeles.)

Fifty patients were studied by all three techniques and were divided into the following categories: I. Occlusive Vascular; II. Aneurysms; III. Trauma; IV. Tumor and V. Carotid tie-off. Control subjects consisted of; 8 healthy hospital employees who had radioisotope cerebrograms only and 7 patients who had all three tests, in whom prolonged observation and other examinations showed no neurological abnormality. The radioisotope cerebrogram, a

graphic presentation of the dilution curves recorded simultaneously from both anterior cerebral hemispheres by external scintillation counting, provides a simple method for detecting differences between the vascular patterns of the two hemispheres. A precordial dilution curve run simultaneously gives an index of cardiac output in relation to cerebral blood flow. The arteriograms and cerebrograms show a close correlation when the pathology is in the region of the Circle of Willis or proximal middle cerebral artery. The cerebrogram aids in the interpretation of the arteriogram by showing the functional significance of structural defects. The EEG was informative mainly in cases of direct cortical involvement.

C 2. *"Localization of Brain Tumor with I^{131}-Labeled Polyvinylpyrrolidone."* W. Newlon Tauxe, Paul J. Pitlyk, Richard E. Sedlack, Frederick W. L. Kerr, and Hendrik J. Svien (Mayo Clinic and Mayo Foundation, Rochester, Minnesota.)

During study of the metabolism of macromolecular substances, it was found that I^{131}-labeled polyvinylpyrrolidone (PVP-I^{131}) at a molecular weight of approximately 40,000 was not taken up significantly by either muscle, bone or brain tissue. Moreover, it was cleared fairly rapidly from the blood (initial [T/2] = 8 hours) principally by the liver and kidneys. Thus, it appeared that if the vascular permeability of brain tumors would permit its passage, it might be highly suitable as a localization agent for scanning purposes.

Of the first 100 patients suspected of having brain tumor who were scanned with 500 μc. of PVP-I^{131}, 31 of 33 tumors that were subsequently proved histologically were localized correctly; this group included five infratentorial neoplasms, all of which were correctly localized. In an additional 20 cases, an independent presumptive diagnosis of tumor was made on strong clinical grounds and the scanning gave positive results in all of these; this group also included five infratentorial lesions. In the remaining 47 cases, scanning gave negative results. The subsequent clinical courses have not been those of brain tumor.

Brain scanning with PVP-I^{131}, compared with other modes of scanning, would seem to possess the advantage of less radiation than that from Hg^{203}-containing compounds, and a higher rate of positivity, particularly in infratentorial lesions, than has been obtained with other I^{131}-labeled compounds.

C 3. *"The Results of 350 Brain Scans with Radioactive Mercurial Diuretics,"* D. Bruce Sodee (Walter Reed General Hospital, Washington, D.C.)

In the past 18 months we have performed 350 brain photoscans, primarily for the localization of space occupying lesions of the brain. Utilizing 700 microcuries of mercury^{197} Neohydrin or mercury^{203} Neohydrin intravenously, our brain scanning procedure is started one hour post dose. Using two positions, these scans can be completed in approximately two hours. We have found contrast enhancement photoscanning to be an extremely easy method to find abnormal localizations of mercury. Our percentage of missed lesions is extremely low, and our correlation with neurosurgical findings has been excellent. This technique is extremely well suited to primary or metastatic tumor localization and subdural hematoma localization. Our presently utilized mercury^{197} Neohydrin has been proven to be an excellent scanning isotope and delivers 1/100 the radiation dose of mercury^{203} to the kidneys.

C 4. *"Scintillation Scanning of the Kidneys with Neohydrin-Mercury 203."* Frederick J. Bonte, Fred W. Riley, Vernon V. Kirby and Terry D. Allen (The Departments of Radiology and Surgery, Section on Urology, The University of Texas Southwestern Medical School and Parkland Memorial Hospital, Dallas.)

The diuretic Neohydrin may be tagged with mercury 203, a tracer whose gamma emmissions make it highly suitable for deep-organ scanning. The tracer is given in amounts of 100-150 microcuries, and comes to satisfactory equilibrium within the kidneys in one hour. Scans on about 100 patients have been made with modified commercial equipment and are

produced as both photoscans and background-eliminator-processed solenoid print records. The test seems to have little to offer not already available in roentgen contrast procedures for the differential diagnosis of renal cysts and tumors, but, early in its use, seems to promise a good deal in evaluation of renal function. Difference between the functions of the two kidneys have been observed, and active renal mass within a single kidney can be estimated on the basis of tubular accumulation and retention of tracer-tagged Neohydrin. When other methods have proven unsatisfactory, scintillation scanning of the kidneys may be used to clarify anomalies of position, and the kidneys may be localized in the presence of space-occupying lesions.

C 5. *"The Evaluation of Renal and Cardiac Dynamics with the Autofluoroscope."* MERRILL A. BENDER, and MONTE BLAU (Department of Nuclear Medicine, Roswell Park Memorial Institute, Buffalo.)

The autofluoroscope is capable of visualizing compartments within organs. It can also quantitate a rapid change in the concentration of gamma emitting isotopes within these compartments.

The flow of I-131 Hippuran through the renal cortex medulla and pelvis has been evaluated in a number of patients having a variety of renal problems. These "compartmental renograms" were then compared with conventional renograms. Abnormalities in the latter could then be related to an abnormality in a specific region within the kidney.

Barium-137m, with a 2.6 minute half-life, delivers 1 mr. total body radiation for each millicurie administered intravenously. Up to 100 mc have been administered antecubitally and through cardiac catheters with cinegraphic recording of the passage of this bolus through the chambers of the heart.

D 1. *"Therapeutic Intralymphatic Infusion of Radioactive Isotopes."* IRVING M. ARIEL, MICHAEL R. RESNICK, and DONNA GALEY (Pack Medical Foundation and Hospital for Joint Diseases, New York.)

An ideal means of irradiating lymph nodes is by the intralymphatic infusion of different radioactive isotopes: this has been utilized to treat patients with lymphosarcoma and Hodgkin's disease, patients with seminoma of the testis, and others with malignant melanoma. The isotopes used have been Au^{198} and Y^{90} micro-microspheres (3M). The latter are ceramic microspheres measuring 1 to 4 microns and are trapped by the first echelon of lymph nodes. They have been found most useful for treating such lesions as melanomas of the hands and feet which are suspected of having metastasized to regional lymph nodes. The other isotope utilized has been I-131 ethiodol which has been utilized for irradiating larger groups of lymph nodes such as the retroperitoneum, for lymphomas and seminomas. The results of these efforts, which include radioautographs, sciniscans, lymphograms before and after radioisotope therapy, metabolic studies of the fate of the isotopes, and the histologic effects of the irradiation, will be presented.

D 2. *"The Therapeutic Use of Radioactive Gold Seeds in Neoplasms."* PAUL LACHANCE and A. F. VALLÉE (Department of Radiology, Hospital Sainte Jeanne D'arc, Montreal.)

The authors present sixty cases of the application of radioactive gold Seeds in miscellaneous neoplasms including bladder tumors, local recurrences of breast and uterus neoplasms, cancer of the tongue and buccal cavity, and other various localized tumors.

They describe the equipment and technique employed, stressing on the indications and advantages of this method.

D 3. *"Properties and Medical Uses of Radioactive Ceramic Microspheres."* T. N. LAHR, C. J. HALVA, and J. P. RYAN (3M Nuclear Products, St. Paul.)

Medical interest in the diagnostic and therapeutic applications of insoluble radioactive compounds of small particle size has been active since the introduction of Au-198 colloid in

1946. However, the number of isotopes available to the clinician has been limited to those with chemical properties suitable for preparation in an insoluble form. The ceramic microspheres described herein can be labelled with essentially any radioisotope, with specific activities of hundreds of curies per gram in some cases. Further, once the isotope is immobilized by this technique it is metabolically inert, remaining almost completely at the site of injection or administration. In general, less than 0.1% of the radioactivity associated with the microspheres is soluble when they are soak-tested in dilute acids for periods of seven days or more.

The microspheres are completely ceramic in nature, having a melting point in excess of 1000°C, and are insoluble in all common reagents, with the exception of hydrofluoric acid. They can be prepared in various controlled particle size ranges from 10-100 microns and larger. The standard materials have a nominal diameter of 15, 35, 50 and 80 microns and range within ±20% of this size. Non-spherical microparticles, of the same chemical nature as the microspheres, are available in the 1-5 micron range. Due to the inorganic nature of these materials no radiation damage to the microspheres is apparent even at doses up to 10^9 rad.

Clinical evaluation of this material is being done by several groups in the U. S. and Canada. Diagnostic uses include examination of organ blood supply, determination of A-V shunts, and others. Evaluation of microspheres (principally labelled with Y-90) for tumor therapy has been in progress for about two years with somewhat encouraging results.

D 4. *"Intragastric Irradiation with Ru-Rh^{106}; Results with Fractional Dosage in Patients with Peptic Ulcerative Disease and with Gastric Neoplasms."* ROBERT C. FRUIN, MARGARET S. LITTMAN, and ARMAND LITTMAN (Department of Gastroenterology and Medical Service, Veterans Administration Hospital, Hines, Illinois.)

Using a small cylindrical source of Ru-Rh^{106}, affixed to a slide wire assembly and mounted within a rubber balloon, we have given intragastric beta irradiation in 6 courses to 5 patients with peptic ulcerative disease, and to 6 patients with gastric neoplasm. Two patients with ulcerative disease who had doses of 1000 rep or more developed typical radiation gastric ulcers. One patient given 1600 rep in 8 treatments developed a sustained depression of Histalog-stimulated gastric acidity parallel with an excellent clinical result. There was no evidence of radiation ulcer in 21 months of close observation. In 6 patients with gastric neoplasm doses of up to 2000 rep were given without appreciable influence on the clinical course. In one instance a dose of 600 rep could possibly have slowed tumor growth for several years. We conclude that intragastric irradiation with a point source is feasible. It was not predictably effective in ulcer disease and there was appreciable risk of inducing irradiation ulcer.

D 5. *"Internally Administered Y^{90}-DTPA in Preparation for Homografting of Tissues in Dogs and Man."* H. S. WINCHELL, M. POLLYCOVE, W. D. LOUGHMAN, J. H. LAWRENCE (Donner Laboratory, University of California, Berkeley.)

Relatively selective irradiation of lymphatic structures can be obtained using Y^{90} chelated with diethylene triamine pentaacetic acid (DTPA) in a manner developed in our laboratory. This selectivity has been utilized in preparing dogs for homografting of bone marrow, skin and kidneys and in humans concomittant with homologous bone marrow transplantations in the treatment of acute lymphoblastic leukemia. Following a lethal dose of Y^{90}-DTPA dogs survive if given autologous or homologous bone marrow with hematological evidence for growth of the graft. Prolonged survivals of renal homografts have been achieved using this procedure in dogs. In four patients with acute lymphoblastic leukemia treated by this method, temporary remissions were obtained in each case with no deaths attributable to the procedure itself. Thus far, no definite evidence for homologous marrow "takes" has been noted in the humans treated in this manner.

D 6. *"Intralymphatic Administration of Radioisotopes to Lymph Nodes."* TAKASHI HONDA, JOHN J. RAFTER, GRANVIL C. KYKER (Oak Ridge Institute of Nuclear Studies, Oak Ridge.)

We have administered selected radioactive preparations to 50 or more dogs by intralymphatic injection to compare their localization in lymph nodes. The study is applicable to the problem of nodes that contain minute malignant lesions and that are not removed during surgical treatment. According to radioisotopic characteristics, preparations that localize effectively offer a therapeutic approach by selective irradiation and offer diagnostic detection by external scanning or internal probing to guide surgical treatment.

Radioactive preparations were injected into a lymphatic vessel made visible in the hind foot of a dog by a previous interstitial injection of Indirect Sky Blue between the toes. Through an incision in the dorsum of the foot, lymphatic vessels containing the blue dye are clearly seen lying alongside other major vessels. Soluble preparations (Au^{198}, Ce^{144}, Y^{90}, chelates, etc.) are conveniently injected through a 27-gauge needle fitted to polyethylene tubing (PE-20). Observations at prescribed intervals include measurements of distribution and excretion, scintigrams by external scanning, and, occasionally, radiography.

In general, very small chemical doses (Y^{90}, 10^{-11} M/kg) prepared from a Sr^{90}-Y^{90} generator (Brookhaven) fail to localize adequately and distribute widely somewhat like intravenous doses. Larger chemical doses (stable yttrium, 10^{-7} M/kg) localized better in lymph nodes; however, animals varied considerably. Results with colloidal Au^{198} suggested the used of larger particles. By contrast, ceramic microspheres (50 μ dia.) containing Ce^{144} and suspended in Carbopol (3 M Co.) localized largely in the first lymph node of the stream. We are comparing chelates of these elements that differ in stability to find a suitable preparation between these extreme behaviors. Preliminary results from this last phase of study encourage our continued efforts.

E 1. *"A Comparison of the Distribution of Au-198, I-131 Rose Bengal and Mo-99 in Normal and Abnormal Liver Tissue in Rats."* CHARLES T. KNORPP, LEO COUSINEAU, MARY H. RENNIE, and JOVILLA MANNARD (Radioisotope Service, Veterans Administration Hospital; Internal Medicine, University of Michigan, Ann Arbor.)

It has been determined by Dr. Leif Sorensen that Mo-99 incorporated into the enzyme Xanthine oxidase is concentrated in the liver in sufficient amounts to be detected by a scanner.

Rats bearing palpable intra and extra hepatic Morris 5123 hepatomas were injected intraveniously with Collidal Au-198, I-131 tagged Rose Bengal and carrier from Molybdenum-99. After a suitable period the rats were scanned with a photo scanner, sacrificed and their organs assayed for the concentration and distribution of the various isotopes.

Scans of the rats with extra hepatic tumors showed no concentration of the Au-198 or Rose Bengal while the Molybdenum appeared to be localized in the tumor in the same concentration as in the liver.

Radio assay of the organs confirmed this observation. In all cases the Molybdenum concentration in the tumors and in normal liver tissue was at least 2 fold over that of the other organs assayed. The organs with metastis from the hepatoma showed a high activity of Mo-99.

The greatest concentration of Rose Bengal was in normal liver, while Au-198 showed decreasing concentration from liver to spleen to tumor.

Au-198 and I-131 Rose Bengal are useful in liver scans but both isotopes are lacking in the ability to define small discrete space occupying lesions with present scanning equipment because of their high gamma energy. The relatively weak 0.14 mev gamma ray emmitted by the Te-99 daughter of Mo-99 is easily collimated to allow good resolution by the focusing collimators of the scintillation probes used today. Space occupying lesions or non-functioning liver tissue that may be overlooked because of the penetrating power of the gamma rays of Au-198 and I-131 should be more easily detected, as the normal liver beneath the suspected area should not mask the cold spots; it appears from scans and radio assay of the organs that Mo-99 might be useful in the diagnosis of hepatoma.

E 2. *"Improved Liver Scanning with 6-Hour Tc^{99m} in Fat Emulsion."* P. V. HARPER, K. A. LATHROP, and R. J. MCCARDLE (Department of Surgery, University of Chicago, Chicago.)

While the gain in quality of liver scans with better hardware is extremely difficult and expensive to achieve, there is still considerable room for improvement of resolution without increase of radiation dosage by using some more appropriate isotope as a radiation source. 6-hour Tc^{99m} is available as the daughter of 2.6 day Mo^{99} from which it can be separated with ease. Since it has no particle radiation except conversion electrons and a clean 140 Kev gamma (HVL $\sim$ 4.5 cm), it is very suitable as a scanning agent. The radiation dosage is extremely low so that millicurie quantities may be given safely. In the form of the thiocyanate, it is soluble in fat solvents and fat and may be incorporated with ease in commercially available intravenous fat emulsions such as "Lipomul" in which form it goes largely to the liver where it has approximately a 12-hour biological half life. With one millicurie of Tc^{99m} tagged Lipomul intravenously, a liver scan 4 hours later gives maximum count rates up to 5000 c.p.m. using the 31 hole collimator of the Picker Magnascanner, primarily designed for thyroid scanning. The resolution of the resultant scan is correspondingly increased and the estimated radiation dosage to the liver is about 300 millicuries.

E 3. *"The Comparison of Colloidal $Gold^{198}$ and Colloidal $Gold^{199}$ For Liver Scanning."* JAMES H. CHRISTIE, and WILLIAM J. MACINTYRE (Highland View Hospital, Cleveland.)

In liver scanning, wherein we are attempting to localize voids in an area of extended activity, we are confronted with serious problems in shielding and collimation. It is of interest therefore to determine whether colloids of lower energy materials would improve our ability to demonstrate lesions within the liver.

To accomplish this a comparison was made between Colloidal $Gold^{198}$ (411 keV) and Colloidal $Gold^{199}$ (158 keV). This comparison included an evaluation of the colloids by uptake and removal measurements and animal distribution studies. The effect of improved collimator efficiency versus restriction by tissue absorption was accomplished through phantom studies. The actual comparison of patient scans will be presented along with a discussion of radiation dose.

E 4. *"Radioisotope Photoscanning and Hemodynamic Pattern of the Liver in Hepato-splenic Schistosomiasis."* MUHAMMAD ABDEL RAZZAK (Cairo University and A.E.E., U.A.R.)

In normal individuals, serial blood samples proved to be the best method for determination of hepatic blood flow; since disappearance of colloidal radio-gold was a single exponential function of time. In contradistinction, this did not hold true in hepato-splenic bilharziasis. The hepatic uptake method appears to be more reliable, due to hyperplasia of reticulo-endothelial structures in the enlarged spleen and due to occurence of various types of vascular anastomosis.

In the present work, the half time for hepatic accumulation of radioactivity was estimated by both colloidal gold ($T_{1/2}$ G) and rose bengal ($T_{1/2}$ R.B.), permitting calculation of the clearance fraction ($T_{1/2}$ G/$T_{1/2}$ R.B.). Furthermore, the cardio-portal circulation time (CPCT) was measured by RISA and hepatic photoscans obtained using radiogold.

In mild cases, all these tests were normal. Whereas in moderate cases, both $T_{1/2}$ G and $T_{1/2}$ R.B. and CPCT were slightly longer and photoscans showed some diminution in density. With the appearance of oesophogeal varices, these changes became much more marked, with little change in clearance fraction; denoting that the main effect is diminution in liver blood flow. In cases with ascites, photoscanning showed evidence of severe cirrhosis. The hemodynamic pattern was variable. CPCT was in many cases shorter than normal. $T_{1/2}$ ranged between

normal and very high values, with marked reduction of clearance fraction in % of these cases; denoting that hepato-cellular affection is late and inconstant. Moreover, ascites seems to be multifacorial in origin; the main factor being portal hypertension, hepatocellular dysfunction, hypoproteinemia and/or otherwise.

E 5. *"The Use of Hg-203 Labeled Bromomercurihydroxypropane (BMHP) in Radioisotope Scanning of the Spleen."* HENRY N. WAGNER, JR., JOHN G. MCAFEE, IRWIN M. WEINER, MASAHIRO IIO, JOSE MARTINEZ, and WINSTON P. CAINE, JR. (The Johns Hopkins Medical Institutions, Baltimore.)

Under a variety of experimental and pathological conditions, moderately damaged red blood cells are removed from the circulation by the spleen, whereas severely damaged cells are removed by the reticuloendothelial system as a whole. In the past, thermal damage has been the principal means of damaging Cr-51 labelled red cells for the purpose of visualizing the spleen by scintillation scanning. In surveying a variety of mercurial sulfhydril inhibiting compounds, Kessler and Pitts (1957) noted that iodomercurihydroxypropane concentrated in the spleen of dogs following its intravenous injection. On the chance that the splenic concentration might be the result of binding of the mercurial by red blood cells with subsequent splenic sequestration of the chemically-damaged cells. Hg-203 bromomercurihydroxypropane was synthesized and investigated. The following conclusions can be drawn from the preliminary data: (1) Of all mercurial sulfhydril inhibitors studied, BMHP is the most avidly bound to red blood cells; 98 per cent of the radioactivity is bound to the red cells even after repeated washing of the cells; (2) red cells labelled with BMHP in the presently available specific activity (296 mc./mg.) are moderately damaged as evidenced by their rate of clearance from the circulation; (3) the spleen is the primary site of accumulation of the Hg-203 BMPH labelled cells; (4) this compound, or its Hg-197 analogue, offers advantages over the technique of splenic scanning, using Cr-51 labelled, heat damaged red cells.

E 6. *"Renal Uptakes and Renal Scanning with Radioactive Mercury^{197} Neohydrin and Mercury^{203} Neohydrin."* D. BRUCE SODEE (Walter Reed General Hospital, Washington.)

In Europe for the last several years radioactive mercurial uptakes have been done to differentiate unilateral renal disease. Recently the Johns Hopkins group reported some success in the differentiation of unilateral renal disease by measuring the differential uptake of mercury^{203} Neohydrin in the renal areas. We have started a long-term project of comparing the differential uptake of mercury^{197} Neohydrin and mercury^{203} Neohydrin. Iodine^{131} Hippuran renograms and repeated renal scanning procedures in comparison with other standard renal studies in the localization of renal artery disease and renal parenchymal disease are also being carried out. At the present time we have completed 25 normals, and these will be compared with 100 patients sent to us for routine hypertensive evaluation. The technique and preliminary results will be presented.

F 1. *"The Response of Disseminated Reticulum Cell Sarcoma to the Intravenous Injection of Colloidal Radioactive Gold."* PHILIP RUBIN, and SEYMOUR H. LEVITT (Division of Radiation Therapy and Isotopes, Strong Memorial Hospital, Rochester, New York.)

Two cases of reticulum cell sarcoma are reported in which intravenous colloidal gold was used in late stages of the disease. The rationale for the use of colloidal gold in this disease was that the distribution of the disease and the colloidal gold would be the same since the colloidal gold is phagocytized by the reticulum endothelial cells from which the malignant reticulum cells originally arise. The results of the treatment are discussed and evaluated.

In cases of reticulum cell sarcoma which have diffuse minute neoplastic involvement of the liver, spleen and possibly minimal bone marrow involvement, the use of IV colloidal radio-

gold may be justified as an experimental approach. No more than 50 mc. should be used. This approach should not be used with evidence of bone marrow depression and is not useful where large discrete neoplastic masses or lymph node involvement predominates.

F 2. *"Triiodothyroidism—Clinical Problems."* P. CZERNIAK and S. CHAITCHIK (Government Hospital Tel-Hashomer, Radium and Isotope Institute, Israel.)

Thyroid cases with laboratory and clinical discrepancies were studied. We eliminated the possible known laboratory errors and the errors due to artificial results of the iodine-131 studies. (KSCN + IST (Iodine Suppressing Test) + EST (Estrogen Suppressing Test) + TSH test:) A careful clinical examination was also performed. A group of thyroid cases was eliminated, in whom occurred an abnormal hormonal secretion of triiodothyronine only. Clinically, they are labile border line or slight hyper- or slight hypo-thyroid patients, with an enlarged diffuse or nodular thyroid in some cases.

On the laboratory examinations a high PBI, a normal BMR, a normal iodine uptake, an elevated Conversion Ratio, and a low Butanol Extract—were found. The conclusive findings were established on the radiochromatography and in the results of I^{131} Triiodothyronine-uptake by the RBC. These examinations can be carried out in every good equipped clinical isotope laboratory. The radiochromatography shows the existence of triiodothyronine (Rf = 0.74-0.78) but not of tetraiodothyronine, and often of other abnormal compounds of a more elevated Rf. The Hamolsky-test is abnormally elevated, reaching from 17.5 to 31 per cent.

8 similar cases were studied, women and men in different age groups. Three of them were supposed to be border line cases, 3 hyperthyroid, and 2 slight hypothyroid. The treatment with thyroidea sicca in different doses gives satisfactory results. The patients became less labile and the thyroid enlargement regresses.

Pathogenically there exists probably an enzymatic disfunction which results:

1. in the impossibility to achieve thyrosine-thyronine iodine binding into thyroxine;
2. in the production of abmormal amounts of triiodothyronine, or in the quick transformation of tetraiodo on triiodothyronine before its entry into the blood stream;
3. in the production of other abnormal protein bound compounds.

These hormonal disorders cause an elevated PBI and C.R., a low Butanol Extract, an elevated I^{131} TRI erytrocytes uptake, and TRI^{131} spot on the chromatography.

The amount of the produced triiodothyronine can be variable. The biological half life of this hormone is short. This two features explain why the clinical states of the patients with a selected TRI secretion are variable and labile ones.

F 3. *"Determination of Protein-Bound Iodine (PBI) is Human Plasma by Thermal Neutron Activation Analysis."* EDWARD M. SMITH, JAMES M. MOZLEY, HENRY N. WAGNER, RICHARD REBA (National Institutes of Health, Bethesda; Johns Hopkins Medical Institutions, Baltimore; Division of Nuclear Medicine, Walter Reed Army Institute of Research, Washington.)

Neutron activation analysis, a method of identifying and quantitating an element by measuring the characteristic radiations induced by neutron bombardment, was found to be a precise, rapid and potentially practical clinical method for measuring PBI. Pre-irradiation passage of human plasma through ion-exchange resins in the ammonium acetate form removed greater than 99.9% of the inorganic iodide as well as most other inorganic ions. Neutron bombardment of the treated plasma in a nuclear reactor with a flux density of approximately 10^{11} thermal neutrons/cm^2/sec. activated I^{127} (thyroxine) to its isotope, I^{128}. After irradiation, major radiochemical impurities were eliminated by simple radiochemical techniques (stable isotope dilution and differential precipitation). The induced I^{128} radioactivity was measured and compared to activated iodide standards by gamma-ray spectrometry using spectrum stripping. For 43 duplicate determinations the sample mean difference was 0.31μg of I/100 ml. of

plasma ± 0.24μg of I/100 ml. of plasma. Studies in which varying amounts of thyroxine were added to plasma yielded recoveries of (average of 5 determinations): 0.68μg/100 ml. added, 0.73μg/100 ml. found; 1.35μg/100 ml. added, 1.25μg/100 ml. found; 2.70μg/100 ml. added, 3.01μg/100 ml. found and 5.39μg/100 ml. added, 5.04μg/100 ml. found. In 48 determinations the results of the method developed in this work paralleled the modified Barker method, yielding the regression line: $Y = 7.97 + 1.09\ (X - 6.17)$, where Y is the value of PBI by activation analysis and X is the value by the modified Barker method. The difference of 29% ± 11% in the mean values of these results is similar to the difference between the Zak (wet washing) and Barker chemical methods. Advantages over present chemical methods are technical simplicity, elimination of the protein digesting step, elimination of the reagent blank and a significant reduction in the iodide contamination problem.

F 4. *"A Clinical Comparison of a Test of Thyro-Binding with the Standard PBI."* JOHN F. SCHOLER (Palo Alto Clinic, Palo Alto, California.)

A simple test of thyroid function which depends upon the thyroxine-binding capacity of serum or plasma has previously been described. The test is easier to do than the other in vitro test, the more commonly used PBI. Since the tests may be used similarly, we have compared the two tests by studying their effectiveness when used clinically.

The results of 2,359 consecutive tests of thyro-binding (TBI) and 1,516 consecutive PBI's were correlated with the clinical thyroid status of each patient as finally determined by his own physician. All tests were done as part of the study of private patients, and in making the final clinical evaluation, the physician's decision was based upon his clinical judgment and at least one thyroid function test such as the BMR, the I 131 uptake, the PBI, and the TBI. Of those patients having the TBI test, 92% of the hyperthyroid patients, 89% of the euthyroid patients, and 96% of the hypothyroid patients had test results within the expected ranges. Of those patients having PBI tests, 5% had values that showed obvious iodine contamination; of the remainder, 89% of the hyperthyroid individuals, 92% of the euthyroid individuals, and 92% of the hypothyroid individuals showed test results within the expected ranges. On this basis, the test appeared to be equally valuable as a clinical aid, the TBI having the advantage of not being subject to iodine contamination.

F 5. *"The Resin Sponge Modification of the T-3 Test."* GEORGE B. MCADAMS, and RALPH F. REINFRANK (Department of Pathology and Department of Medicine, Hartford Hospital, Hartford.)

A variation of the T-3 test is described which employs a resin similar to that in the Scholer method but pre-incorporated in plastic sponges (Triosorb—Abbott Laboratories). The measuring of aliquots of resin is thereby eliminated. After an hour's incubation at 25°C with I^{131}-T3 (0.1 uc/ml.) and 1 ml. of serum, the subsequent washing of the sponge is unusually simple to perform and the residual radioactivity in the sponge counted in the original tube, thus doing away with the transfer step.

The results are reported as % uptake by the resin sponge. The normal range was established as 25-35% on the sera of forty-nine laboratory personnel (mean 29.86%, one standard deviation—2.48). A pooled serum is tested each day and averages 32%. A correction for the day's run is made whenever the pool is beyond arbitrary limits of 31 and 33%.

Sixty patients have been evaluated clinically by the Wayne index and the resulting groups correlated with ankle reflex time, PBI, RAI uptake, BMR and T3 resin sponge uptake.

A larger series had been previously analyzed in relation to the erythrocyte T3 uptake. Better separation of the hyperthyroid group occurs with the resin sponge modification while both reveal considerable overlap of the hypothyroid groups in the normal range.

Over 1,000 determinations have been made in the last 8 months of 1962. The method retains all the advantages of the Scholer technique over the rbc uptake and is even easier and quicker to perform.

G 1. *"Gastric Photoscans with Colloidal Aggregates of Radioalbumin (Mechanism, Diagnostic and Therapeutic Implications)."* GEORGE V. TAPLIN, DELORES E. JOHNSON, EARL K. DORE, and HARRIET S. KAPLAN (Laboratory of Nuclear Medicine and Radiation Biology, UCLA Medical School, Los Angeles; Nuclear Medicine Division, Department of Radiology, Los Angeles County Harbor General Hospital, Torrance.)

The stomach may be visualized by photoscanning following intravenous injection of inorganic radioiodine or of colloidal aggregates of human serum albumin I^{131}. Iodide is known to concentrate in the gastric mucosa and salivary glands to about the same degree as in the thyroid. There is gastric recycling for several hours because iodide is excreted relatively slowly in the urine, is not absorbed from the stomach but is rapidly absorbed from the small intestine. Albumin is also known to be secreted in the gastric juice and degraded by enzymatic digestion. Photoscans after I.V. injection of colloidal aggregates of albumin I^{131} or NaI^{131} demonstrate the extra thyroidal sites of iodide metabolism.

Some gastric carcinomas are known to concentrate iodide 2-30 x more than the normal gastric mucosa. In such instances the diagnostic and therapeutic potentialities are obvious. X-ray photoscans of normal subjects, and patients with various gastric lesions will be presented.

G 2. *"Diagnosis of Pancreatic Disease by Photoscanning."* THOMAS P. HAYNIE, ALBERT C. SVOBODA, and GEORGE D. ZUIDEMA (Division of Nuclear Medicine, University of Texas Medical Center, Galveston; Department of Internal Medicine and Department of Surgery, University of Michigan Medical Center, Ann Arbor.)

The results of pancreas photoscans performed with Se75 selenomethionine in 14 patients subsequently operated upon have been reviewed in an attempt to assess the reliability and usefulness of this procedure in the diagnosis of pancreatic disease. The pancreas was well visualized in 5 out of 8 patients without gross abnormality of the pancreas at the time of exploratory celiotomy. In 5 out of 6 patients with a variety of pancreatic diseases, abnormalities consisting of diffuse decrease in concentration or local abnormalities were observed. The procedure proved useful in localizing tumors in the pancreas, evaluating the patency of the pancreatic ducts, and in the diagnosis of pancreatitis. Certain difficulties with interpretation brought about by variations in the normal size, shape and concentrating ability of the pancreas and interference from radioactivity in the liver were encountered and are expected to limit the diagnostic accuracy of the procedures. In spite of its limitations at the present time the technique does offer the only method for directly visualizing the pancreas short of an operation and deserves further application.

G 3. *"Clinical Experience with F-18 and Sr-87m for Bone Scanning."* MONTE BLAU, YEHUDA LAOR, MERRILL A. BENDER (Department of Nuclear Medicine, Roswell Park Memorial Institute, Buffalo.)

The short lived isotopes Fluorine-18 (reactor produced) and Strontium-87m (milked from Yttrium-87) localize in bone lesions when administered in simple ionic form. These isotopes have physical advantages over Ca-47 and Sr-85 for bone scanning. In addition, because of the rapid clearance of non-localized fluoride ion, the visualization of bone lesions with this agent is particularly effective.

A clinical series will be presented including cases with visualization of bone lesions before x-ray changes have appeared.

G 4. *"Early Diagnosis of Metastatic Bone Cancer by Photoscanning with Strontinum-85."* N. David Charkes, and David M. Sklaroff (Albert Einstein Medical Center, Northern Division, Philadelphia)

Roentgen diagnosis of metastatic cancer to bone has been impeded because bone calcium content must be altered by 30-50% before visible changes can be appreciated. Radioisotopes of calcium, phosphorus, gallium, fluorine, and strontium are deposited in normal bone and accumulate in areas of increased osteogenesis in greater than normal quantity. Strontium-85, a pure gamma emitter (0.513 MeV) has been shown to accumulate in areas of bone metastases prior to observable roentgenologic changes, thereby providing a means of early diagnosis of disseminated cancer to bone.

Forty patients with cancer and proven or suspected bone metastases were scanned 24 to 48 hours after the intravenous administration of 50 μc of Sr-85. In general, there was good correlation between the photoscan and the X-Ray, but in many instances the photoscan revealed more extensive disease than could be visualized on roentgenogram. Bone biopsies were obtained in 9 patients from scan-positive areas, and confirmed the scan findings by the histologic demonstration of tumor. In a few instances, negative scans were obtained in patients with osteolytic lesions, particularly in ribs. Phantom studies were conducted to evaluate the efficiency of the method.

The Strontium-85 photoscan is a reliable method of early diagnosis of metastatic osteoblastic cancer to bone prior to observable roentgen changes and in the absence of symptoms. The strontium scan has aided the radiation therapist in planning treatment portals.

G 5. *"Kinetic Studies of Calcium Based on Saliva and Total Body Retention Measurements of Sr^{85} and Ca^{47}."* Ernest Greenberg, Mario Merlino, David Weber, Karen Corey, Peter Kenny, and John Laughlin (Sloan-Kettering Institute, New York.)

Using Ca^{47} or Sr^{85} as radioactive tracers for calcium the calculation of the rate of accretion and of the size of the exchangeable calcium pool in man has, until now, been based upon the measurement of the daily excretion of these isotopes and the curve of the fall in specific activity of these isotopes in serum.

Using the HEG (High Energy Gamma) scanning system of The Memorial Sloan-Kettering Cancer Center, it has been possible to obtain direct daily measurements of the total body retention (TBR) of these two isotopes separately or simultaneously. In addition, a comparison of the curves of specific activity of Ca^{47} in serum and in saliva performed simultaneously has revealed an excellent correlation between the two.

Thus it has become possible to carry out measurements of the accretion rate and exchangeable pool of calcium without the need for the daily collection and processing of excreta and without resorting to multiple blood letting in non-hospitalized patients.

The techniques and preliminary results of such studies conducted in 5 patients will be presented and discussed.

G 6. *"Localization of Eye Tumors by External Counting Utilizing Mercury^{203} Neohydrin."* D. Bruce Sodee (Walter Reed General Hospital, Washington, D.C.)

The localization of intraocular tumors was first attempted with phosphorus^{32} by Thomas, Krohmer, and Storaasli in 1952.[1] Because of the beta irradiation and difficulties in counting, this isotope was not widely accepted for the localization of eye tumor. Mercury^{203} Neohydrin has been used with success in the localization of brain tumor[2] and we suspected that concentration might also occur in eye tumor. External counting and photoscanning procedures were performed on patients with known eye tumor and results compared with patients having other types of eye disease and no disease.

G 7. *"Quantitative Comparison of Risa and Radio-mercury in Brain Scanning."* WILLIAM FEINDEL, LUCAS YAMAMOTO, and NICHOLAS RUMIN (McGill University and Montreal Neurological Institute, Montreal.)

Radio-mercury in the form of Neohydrin, with a single line gamma emission and rapid clearance from the blood, provides features of advantage over radio-active iodinated serum albumin for brain scanning, but direct quantitative comparison of these two agents in a series of verified intracranial lesions has so far been lacking. We have now made such a comparison, using the automatic contour twin brain scanner with pulse height analysis and a form of registration of the total and differential uptake which retains the quantitative character of the radio-activity without the distortion associated with photoscanning. Effective differential uptake of Neohydrin is developed within three hours in most intracranial lesions after intravenous injection. At that time the local uptake is double that found twenty-four hours after administration of RISA. No significant distinction could be demonstrated on either the time, course or percentage of uptake between meningiomas and glioblastoma multiforme.

H 1. *"Studies on 24-Hour PBI-I^{131} Conversion Ratios by an Ultrafiltration Technique."* AUGUST MIALE, JR., JOSEPH S. BURKLE, PRENTISS M. DETTMAN (U.S. Naval Hospital, National Naval Medical Center, Bethesda.)

The PBI-I^{131} conversion ratio is well recognized as a reliable index of thyroid function. Separation of bound and unbound radioiodine by ultrafiltration appears to offer a rapid and reliable test that is simpler than methods requiring protein precipitation and washing.

Serum ultrafiltrates of patients with a variety of thyroid disorders are prepared 24 hours after ingesting 20 microcuries of radioiodine. The ratio of protein bound to free iodine is determined by counting serum aliquots and ultrafiltrates in a well-type scintillation counter. Data in over 100 cases indicates that the conversion ratio compares well with the clinical diagnosis, and the range of normal values (20-50%) is similar to that determined by other methods. The relationship of conversion ratios measured by ultrafiltration to other thyroid function parameters and sources of error in interpretation are discussed.

H 2. *"A Metabolic Defect Associated with Exophthalmos and Thyroid Disease."* PHILIP C. JOHNSON, TOM R. REDDING, LEO WADE, and JUDA JONA (Radioisotope Laboratory, Methodist Hospital, Houston; Veterans Administration Hospital, New Orleans; University of Kansas, Lawrence.)

Thyrotropic exophthalmos is a perplexing medical problem, the eteology of which remains controversial. We have studied exophthalmic patients to determine if abnormal metabolic pathways are associated with exophthalmos. These studies showed that patients with exophthalmos may have a smaller available metabolic acetate pool than do normals.

To perform these studies, 10 μc of 1-C-14 acetate was given intravenously to fasting subjects following which fifteen breath samples of C-14 O_2 were collected in 0.1 m hyamine during a two hour period with 10 samples collected during the first twenty minutes. Specific activity (dpm/meq) was determined by titration of the hyamine with HCL.

These curves showed that carbon dioxide specific activity reaches a peak value in 8-20 minutes following which there is a gradual exponential decrease in specific activity. Eighteen patients (5 hyper, 4 hypo, and 9 euthyroid) with clinically apparent exophthalmos showed peak specific activities greater than the normal range.

In addition, to the exophthalmic patients, 2 hypothyroid patients under treatment for thyroid carcinoma, 3 euthyroid patients with a diffuse goiter and 3 thyrotoxic patients with nodular goiters showed high peak specific activities. Seven thyrotoxic patients without thyrotoxic eye signs or exophthalmos showed normal curves. Reserpine treatment produced a minor decrease

in peak specific activities in 3 thyrotoxic exophthalmic patients. Other conditions tested produced no change in the curve. These included active acromegaly, TSH injection, cortisone therapy, diet, and fasting.

H 3. *"Evaluation of Potassium Iodide as a Thyroid Suppressive Agent and its Comparison with Triiodothyronine (Cytomel)."* MAXWELL SPRING (Bronx Lebanon Medical Center, Bronx, New York.)

Rossman (unpublished observations) tried and found potassium iodide a satisfactory thyroid suppressive agent. He worked out the technique of its use and dosage. We have used it almost exclusively in our clinic at the Bronx Hospital. All the suppressive tests performed from January, 1959 to January, 1963 were collected and evaluated as to their accuracy in assessing the thyroid status of the patient. There were 65 tests performed on 51 patients. Seventeen patients were clinically euthyroid, though three had hot nodules; thirty-two were hyperthyroid and two were undiagnosed by the time of this report. A fall of 25% or more of the original iodine uptake was considered to be within the normal range.
Results: The suppressive effect in the euthyroids ranged from a 11.9 to 94.1% fall from the original uptake, with a mean of 47.1%. In those patients with the hot nodules the fall was much less than 25%. Of the 32 hyperthyroids, fourteen had suppressive tests prior to treatment. These ranged from +21.7% to a fall of 22.5% of the original uptake with a mean of 3.4% fall. The test confirmed the clinical diagnosis of hyperthyroidism in 100% of the patients. Twenty-three patients had suppressive tests after therapy with radioiodine. (Four of these had the test prior to treatment). The test accurately reflected the clinical status of the patient.
PART II: Potassium iodide was then compared with triiodothyronine (cytomel) in 37 patients, 17 euthyroid and 23 hyperthyroids. Suppression was greater in euthyroid than in hyperthyroid patients. Potassium iodide was found to be more or equally as suppressive as triiodothyronine in the majority of hyperthyroids before and after therapy and in the majority of euthyroids. Potassium iodide is far cheaper and better controlled in its administration to the patient than triiodothyronine. From the results of this experiment it is felt that it is the drug of choice as a test of thyroid gland suppression.

H 4. *"The Use of Radioisotopes in the Diagnosis of Hyperthyroidism in Infants."* C. IMPERATO (Parma, Italy)

H 5. *"An Approach to the Definition of Preclinical Disease."* NORMAND NAUMOFF (Department of Radiology, Wayne State University, Detroit.)

A. The Present definition of disease necessitates
   1) The presence of symptoms which
      a) can be mimiced by normal patients
      b) excludes preclinical asymptomatic disease
      c) are rarely characteristic
   2) Does not give a clear laboratory endpoint between physiological and pathological function.
      a) early disease may be within normal range
      b) laboratory procedures have inherent errors of procedure and performance.
   3) Is not broad enough to include preclinical diagnosis, prevention, define and pattern new disease concepts.

B. It is proposed that the definition of disease be extended to include *any biological system which responds inappropriately to physiological stimuli.* The advantages of defining disease as inappropriate response to stimuli are that it is:
   a) objective
   b) measurable
   c) cross checks baseline findings in the laboratory.

This expanded definition can

1) Differentiate an atypical physiological process from a subclinical pathologic change
2) Further delineate pathologically discrete entities by their response to stimuli to determine etiologies.
3) Clinically obscure or otherwise unapproachable organ systems like the pituitary can be attempted.
4) Utilize pharmacological compounds as stimuli provided the overall cellular environment is not changed.

Examples are presented and cases discussed.

C. Disease as an inappropriate response to physiological stimuli has the following assumptions inherent in its definition.

1) The response to the normal system should be known
2) The stimuli should be of sufficient intensity to change measurably the normal state.
3) The stimulus must be physiologically active to the biological system tested.
4) Therapy should be directed to adjusting the response of the deranged organ system by substitution, replacement, minimizing environmental demands, or by indirect compensation other organ systems.

H 6. *"Analog Computer Simulation of Radioiodine Tracer Studies in Thyroid Disease."* DONALD W. BROWN and ARTHUR L. KRETCHMAR (Medical Divisions, ORINS, Oak Ridge.)

A mathematical model of iodine metabolism will be presented and discussed. The programming of this model on an analog computer will be briefly outlined. Data from illustrative clinical tracer studies will be presented to show how the computer model can be used to derive greater insight into the abnormal physiology underlying the tracer studies illustrated.

H 7. *Studies in Radiomicrobiology: Distribution of I-131 Labeled Staphylococcal Entehotoxin in Young Cat.* C. ARGHITTU, L. LENZERINE, and M. ROSSI-TORELLI (Grado, Pisa, Italy.)

H 8. *"Studies on the Radiobiological Effects of Thymidine-H-3 During its Incorporation into the DNA of Landschutz Ascites Tumor Cell."* J. GROSS (Jerusalem.)

J 1. *"Potassium Changes in the Cardiac Muscle as Studied by a K^{40} Method."* (Preliminary Communication) P. CZERNIAK and I. KARIV (Government Hospital Tel-Hashomer, Israel.)

The natural K^{40} was measured in different amounts of different potassium salts. Finally, we used 200 milligrams-samples of a mixture in various proportions, of chemically pure KCl and NaCl, and a flow counter, for the establishment of a standard curve, which gives us an amount of K according to the counting.

Samples of cardiac muscle (from six sites of the heart), of the liver, of a body muscle and body fat, were taken from necropsied patients. After a physico-chemical processing we received a small quantity of powder from a weighed quantity of a fresh tissue. The radioactivity of this sample was measured by the same flow-counter. We utilized the formerly established curve for plotting the quantity of potassium. Some results were checked by a chemical method in an analytical laboratory. The quantity of K was calculated in mg by gr or fresh tissue. Till now 26 cases were so examined.

From the preliminary results we can conclude:

1. There exist about 3 mg of K per gr of normal cardiac muscle with a small difference in both ventricles. A smaller amount is found in the septum.
2. The amount of K in the liver equals approximately that of the cardiac muscle. More differences are found in the other tissues.
3. An elevated amount of K is found in the site of myocardial infarction (till 13 mg/gr), and in the surroundings (6-8 mg/gr).
4. The ratio between a diseased cardiac muscle and a normal, and between an infarcted place and a non-infarcted one equals 3 and 4. The K changes in serum of the same patient or of different patients cannot be so large. It seems that there doesn't exist any correlation between the amount of K in the serum and in the cardiac muscle.
5. An elevated K was also found in a case of paroxymal tachycardia.
6. A low amount of K (till 1 mg/gr and even less) was found in cachectic, carcinomatous and arteriosclerotic cases.

Further investigations on patients, who were infarcted, disrythmic, hypertensive and hypotensive, will be performed; the amounts of muscular K will be correlated with findings in vivo; the summarized conclusions may be of clinico-pathological-cardiological value.

J 2. *"The Use of Instrumentation to Subtract Blood Pool From Parenchymal Radioactivity for Determining the Hepatic Uptake of I-131 Labeled Fat."* J. R. McLaren, W. B. Miller and W. D. Drew, (Atlanta, Ga.)

J 3. *"The Development of a New Diagnostic Test for Liver Function Using Radioiodinated Benzoic Acids."* Manuel Tubis, William H. Blahd, John S. Endow, and Surjan S. Rawalay (Departments of Radiology and Medicine, University of California School of Medicine, Los Angeles.)

The proposed test is based on the conversion of radioiodinated benzoic acids by the liver and the measurement of the excreted conjugates in the urine.

The authors have prepared the radioiodinated, isomeric, iodobenzoic acids of high specific activity.

Results of the proposed test in normals, and in patients with cirrhosis, hepatitis and other liver pathology will be presented along with correlative data from other liver function tests.

The urinary excretion patterns and rates as well as the characterization of the excreted metabolites have been studied by chromatographic and radioautographic techniques. Removal and elimination from the blood are too slow to permit external counting.

The advantages of the proposed test are: (1) the measurement of the urinary excretion of the radioactive conjugates, if kidney pathology is absent, may provide a simple, rapid, nontraumatic test of liver funtcion; (2) the use of the labeled iodobenzoic acids requires only counting the urine samples thereby eliminating extensive analytical procedures; (3) their use permits stressing the liver with similar agents such as sodium benzoate or with dyes so as to measure other liver functions simultaneously; (4) their use permits the test to be done on patients on low sodium regimes. The use of the labeled acids will permit studies of the processes involved in the metabolism and conjugation of these substrates.

This investigation is supported in part by a research grant AM-06636-01, U. S. Public Health Service.

J 4. *"The Distribution of Rb^{86} in the Dog's Heart."* B. Malamos, S. Mouloupoulos, P. Kostamis, E. Paraschou and K. Ilias (Department of Clinical Therapeutics, University of Athens, Athens, Greece.)

Rb^{86} was administered through a catheter into the left atrium of dogs. The isotope was administered in four single doses of 20 μC each and then as continuous slow infusion of 1 μC per minute.

The β-activity was recorded with a small size counter from the base and apex of the right and left ventricle. Blood samples were taken at regular intervals and the radioactivity of the femoral artery was continuously recorded with an other counter. Small pieces of the myocard were taken at the same sites as above and the activity was counted in a well type scintillation counter.

The distribution of Rb^{86} was thus studied in vivo. The basic finding was a difference in activity between the right and left ventricle and between the base and apex of the two ventricles. The gradient was changing under different circumstances, such as pressure changes in the ventricles and dilatation of the heart.

The same measurements were repeated at several time intervals after ligation of the left coronary artery. The changes following the ligation of the artery, the shock and the terminal conditions of the heart's function will be discussed.

J 5. *"Whole Body Iron Loss Measured with a Gamma Spectrometer."* HIROSHI SAITO, THORNTON W. SARGENT, HOWARD G. PARKER, JOHN H. LAWRENCE (Donner Laboratory, University of California, Berkeley.)

Results of studies of iron loss in normal humans done with a whole body gamma-ray spectrometer are presented. Rates of loss, possible loss routes and uniformity of labelling are discussed, and results are compared to those of other workers.

Eight male subjects received 5 microcuries of Fe^{59} intravenously and the amount of total body radioiron retained was measured periodically for more than six months.

Approximately one day after injection, when the radioiron is maximal in bone marrow, the whole body count falls to 90% of the initial value. Thereafter it slowly rises again as newly labelled red cells are released to the peripheral circulation, returning to an average of 96.5% after two weeks. The rate of radioiron loss did not vary widely among the different subjects for the first 100 days.

The average loss of radioiron during this period was 0.05% per day.

A decrease of whole body count after 100 days was observed. This might be due to an increased but small amount of radioiron loss associated with the death of the first generation of labelled red cells. However, it can be better explained by change of radioiron distribution in the body due to partition between stores and hemoglobin synthesis. Radioactivity appeared in the stool and urine after intravenous Fe^{59} injection was also measured. By the analysis of radioiron loss curves, an average of 130 days for red cell life span was obtained.

J 6. *"Distribution of Iron^{59} in the Rat Following Gastric Administration of Labeled Ferrocene."* ARTHUR F. DRATZ, JAMES C. COBERLY, and JACOB H. GOLDSTEIN (Radioisotope Service, Veterans Administration Hospital; Department of Chemistry, Emory University, Altanta.)

Almost all the elements in the three series of transitional metals have been shown to form organometallic compounds consisting of a metal atom sandwiched between two unsaturated hydrocarbon rings. The unusual chemical stability exhibited by some of these compounds has suggested to us the possibility that they might serve as useful new carriers for tracer activity, either in diagnostic or therapeutic applications.

This is a report of the distribution of Fe^{59} in the rat following the gastric administration of labeled ferrocene (di-π-cyclopentadienyliron) preliminary to evaluating its usefulness and suitability in tracer technique. Within twelve days, over half of the administered activity was recovered in urine, and about 10 per cent in feces. Fat initially contained the highest concentrations of Fe^{59}, but these rapidly decreased more than one hundredfold. Liver activity increased for two days to a concentration higher than that observed in fat; thereafter, liver contained a relatively constant 21 per cent of the administered activity. The Fe^{59} concentrations in whole blood increased throughout the experimental period, while that of the plasma rapidly decreased to essentially zero values. The Fe^{59} concentrations in the remaining tissues were much lower than those of liver, and either remained relatively constant or decreased with time.

K 1. *"The Uptake of Radioactive Cesium and Rubidium by Normal and Infarcted Myocardium."* EDWARD A. CARR, JR., (Nuclear Medicine Unit, Department of Internal Medicine and Pharmacology Department, The University of Michigan, Ann Arbor.)

Though scans of experimental myocardial infarcts presently detect them as "hot" areas, Rb^{86}, Cs^{134}, and Cs^{131} may offer the possibility of demonstrating them as "cold" areas. The present study compares distributions of radioactive Rb and Cs in normal and infarcted canine hearts.

Myocardial infarcts were produced by coronary artery ligation 1-4 days before study. Nine dogs (5 ligated) received Rb and 11 (4 ligated) received Cs intravenously (40-600 μc). Photoscans were made before and after sacrifice, which occurred 30 min.-5 hrs. after isotope administration. Radioactivity of tissue samples was then determined in a well-counter.

The ratio, normal myocardial [Rb^{86}]/blood [Rb^{86}] was > 60 at all times studied. The ratio, myocardial [Rb^{86}]/ hepatic [Rb^{86}] was 1.91 at 30′, falling steadily to 0.81 at 5 hrs. [Rb^{86}] in farcts [Rb^{86}] in the same dog's in normal myocardium averaged 0.60 (std. error $\pm$ 0.12).

With cesium the myocardial/blood ratio was 13.4 at 1 hr., increasing as a straight line function to 43.2 at 5 hrs. Myocardial/hepatic ratio was 2.96, falling to 1.64 at 5 hrs. Two of the four dogs subjected to coronary ligation developed actual infarction; the [Cs] in the infarcts/[Cs] in normal myocardium was 0.08 and 0.42.

Though radiation characteristics are obviously also germane, cesium may have an advantage over rubidium in myocardial scanning, insofar as tissue uptakes are concerned, because of cesium's higher heart/liver ratio. In one dog Cs^{131} has already permitted demonstrations of an area of gross infarction as a "cold" area by scanning *in vivo*.

K 2. *"Coronary Circulation Studies with Rubidium-86."* L. DONATO (Pisa, Italy.)

K 3. *"An Approach to the Scanning of Pulmonary Infarcts."* JAMES L. QUINN, III, JOSEPH E. WHITLEY, SHERRILL A. HUDSPETH, and F. CLAY WATTS (Department of Radiology and Surgery, Bowman Gray School of Medicine, Winston-Salem.)

Pulmonary infarcts were produced by embolus technique in dogs.

Chromium-51 tagged red blood cells, iodine-131 serum albumin and mercury-203 chloromerodrin were investigated for their suitability in delineating pulmonary infarcts. The chromium tagged red cells and serum albumin compounds were found to be less suitable than the mercury compound.

Three groups of experimental animals were examined:

1. Control animals
2. Animals in which the compound was injected one hour after embolus.
3. Animals in which the compound was injected twenty-four hours after embolus.

Chloromerodrin (Hg-203) was injected intravenously and animals were sacrificed at 1, 4, 8, 12 and 24 hour intervals. Radioisotope assay of the lungs, (normal and infarcted), myocardium, whole blood, spleen, liver and kidneys was done.

There was a significant decrease in radioactivity in the area of pulmonary infarction as compared to the uninvolved lung.

The possible application of scintiscanning will be discussed.

K 4. *"Measurement of Pericardial Fluid Correlated with the I-131 Cholografin® Heart Scan.* D. M. SKLAROFF and N. D. CHARKES, (Philadelphia)

K 5. *"Factors Which Activate the Coronary Collateral Circulation. A Study with Radioactive Beads."* HENRY L. JAFFE, ELIOT CORDAY, HARVEY ALPERN, ROBERT BLUM, and MICHAEL MEREDITH (Institute of Research, Cedars of Lebanon Hospital and University of Southern California School of Medicine, and University of California at Los Angeles School of Medicine, Los Angeles.)

Previous studies on autopsied hearts have indicated that the intercoronary anastomosis might be as large as 120 μ. We reinvestigated this question by using radioactive ceramic beads in studies on the beating hearts of dogs. Our findings indicate that the anastomosis does not function until at least three weeks following coronary occlusion. The intercoronary anastomoses are less than 30 μ in diameter.

Radioactive ceramic beads averaging 45 μ in size were injected into one coronary artery of the dog's beating heart and then recovered from adjoining collateral coronary arteries. Before coronary artery ligation only 0.4% of the radioactive ceramic beads measuring from 15 to 30 μ in size appeared in the collateral artery. 99.6% of the beads were found to be trapped in the myocardium. However, three weeks following coronary artery ligation as much as 39.8% of the beads were recovered in the adjoining coronary artery and only 60.2% were trapped in the myocardium.

When we injected radioactive ceramic beads averaging 45 μ in size immediately following artificially produced coronary occlusion, we found that almost none of the beads crossed the barrier between the arteries. This showed that the collateral anastomosis after we produced coronary occlusion was less than 45 μ in diameter. Eight weeks after producing coronary ligation we found that 70 to 100% of the beads passed across the collateral bed.

Radioactive beads did not appear in appreciable quantity in the coronary sinus blood. This would suggest that the beads as small as 15 μ were trapped in the capillaries between the artery and vein, and that direct arterial-venous anastomosis is negligible.

Hypoxemia and nitroglycerin did not increase the amount of radioactive beads which would pass across the interarterial anastomosis.

We conclude that the collateral circulation between normal coronary arteries is less than 15 μ in diameter, but that within three weeks following coronary artery ligation it increases and is larger than 30 μ and smaller than 50 μ. The coronary collateral circulation increased considerably after the eighth week following coronary artery occlusion. So-called coronary dilator drugs do not increase the size of the coronary arterial anastomosis.

L 1. *"The Retention of Strontium-85 in Healthy and Diseased Bones of Patients with Breast Cancer"*. K. R. COREY, E. GREENBERG, D. WEBER, P. KENNY and J. S. LAUGHLIN, (New York.)

L 2. *"Intestinal Transport of Radiolabeled Vitamins."* RICHARD P. SPENCER, and TED M. BOW (Department of Biophysics, and Radioisotope Service, Veterans Administration Hospital, Buffalo.)

The daily requirement for vitamins in man ranges from about 5×10^{-3} gm (ascorbic acid) to 5×10^{-7} gm (vitamin B_{12}—cyanocobalamin). Because of the minuteness of these quantities, and the lack of specific chemical tests at low concentrations, radiolabeled vitamins are the compounds of choice in following vitamin absorption and metabolism. Thus far, only vitamin B_{12} has been extensively explored this way, because of the availability of cobalt radioisotopes. Other vitamins do not contain a metallic moiety, and one is limited to use of H^3 or C^{14} in the molecule (and in rare cases, such as thiamin, S^{35}). Studies, on animals, divide vitamins into 2 general classes: those that pass across the in vitro gut wall against a concentration gradient (the unusual case), and those that do not. Among vitamins passing across the in vitro gut wall by diffusion alone (hamster) are: pyridoxin-H^3, vitamin D_3-H^3, ascorbic acid-C^{14}, and

p-aminobenzoic acid-C^{14}. Biotin (H^3 and C^{14}) however passes the master small gut against a concentration gradient (concentrations on the order of 1×10^{-6} M). The rat gut appears to pass all of these vitamins by diffusion alone. There is some evidence that the gut may not be entirely passive in this process, but may alter the vitamins. Extrapolating to man, recovery of 200 counts/min./0.1 ml plasma, assuming 10% counting efficiency for H^3, would necessitate giving 500 μc of the tritiated vitamin (if it distributed evenly into the entire body water, about 56,000 ml). With an effective half-life on the order of one week, such a quantity of tritium would deliver a dose of less than 0.1 R to the recipient. Hence vitamin absorption studies are feasible in man through use of radiolabeled vitamins.

Supported by Grants A-6025 and A-6416 from the U.S. Public Health Service).

L 3. *"Radiostrontium-87m in Studies of Healing Bone Fracture."* WILLIAM G. MYERS and MICHAEL OLEJAR (The Ohio State University Health Center, Columbus.)

Radiostrontium-87m emits a 388-kev γ-ray during isomeric transition to stable Sr-87, with 2.75-hour half-life. Sr-87m is readily obtainable in extremely high specific activity from yttrium-87 after the latter captures an electron. During simple elution of Sr-87m from a chromatographic column that is easy to make, the residual Y-87 parent remains firmly bound. The 80-hour half-life of Y-87 makes the 2.75-hour daughter readily available in any hospital. The Y-87 parent is generated in a cyclotron either by bombarding strontium with deuterons or protons, or by bombarding rubidium with helium ions.

Relative rates of accumulation of strontium-87m in healing tibia and fibula fractures of young rats were compared with the corresponding areas in the contralateral intact legs after daily intraperitoneal injections of labeled strontium ions. Advantages of Sr-87m for such studies are obvious in comparison with long-lived radioisotopes such as 65-day strontium-85 or 4.9-day calcium-47: 1) The 2.75-hour Sr-87m makes possible studies of dynamic day-to-day changes in relative rates of accumulation because measurements do not include significant residual activities from a previous injection a day earlier; 2) Radiation exposures are greatly decreased; 3) The 0.26-centimeter "narrow beam" half-thickness in lead of the Sr-87m 388-kev γ-ray makes collimation more effective and protection simpler than for the 1,310-kev γ-ray of Ca-47, or even for the 514-kev γ-ray of Sr-85.

Strontium-87m uptakes in the healing fractures were greater than in the contralateral normal bones. The maximum fracture-to-normal ratio of 6.3 was reached two weeks after fracture. The time to maximum uptake in the normal leg was 17-33 minutes, while that in the fractured leg varied with the age of the fracture and reached a maximum 200-260 minutes after injection of the labeled strontium, 12-14 days post fracture.

L 4. *"Retention of Radioisotopes by Hair, Bone and Vascular Tissues."* WILLIAM H. STRAIN, WILLIAM P. BERLINER, CHARLES A. LANKAU, JR., RICHARD K. MCEVOY, CAPT. WALTER J. PORIES, and ROBERT H. GREENLAW (School of Medicine and Dentistry, The University of Rochester, Rochester, New York; USAF Hospital, Wright-Patterson Air Force Base, Ohio; School of Medicine and Dentistry, The University of Kentucky, Lexington.)

Recent studies have shown that after administration of I-131, Sr-90, of Zn-63, significant amounts of the radionuclides accumulate in the hair. Since hair contains many inorganic elements, it is important to know how well this tissue reflects the radioisotopic and stable elements of the body. Accordingly, comparative studies have been made on the retention of vanadium-48 and zinc-63 in the hair, bone, aorta, and other tissues of rats. Vanadium was chosen because it is an inhibitor of cholesterol biosynthesis, is present in microgram quantities, and is excreted largely in the urine. Zinc, a growth and puberty factor present in the body in amounts nearly equal to iron, is excreted largely by the pancreas.

After intravenous administration to rats, vanadium-48 hair retention parallels the vandium

retention values of the other tissues. Zinc-63 continues to increase in the hair with passage of time, and the hair retention values can be related only to bone. Both isotopes are retained significantly by vascular tissue. Although additional work with other radionuclides is needed, it appears that hair reflects the radioisotope content of bone satisfactorily, and may provide a non-destructive method of evaluating the bone burden. The correlation of the radioisotope content of hair and vascular tissues is complex and a satisfactory relationship seems to exist only for elements that are excreted in the urine.

L 5. *"Selective Isotopic Labeling of the Parathyroid Gland."* E. JAMES POTCHEN and JAMES B. DEALY, JR. (Harvard Medical School, Department of Radiology, Peter Bent Brigham Hospital, Boston.)

A primary function of the parathyroid gland is the formation of polypeptide or small protein hormones which have been analysed chemically by Rasmussen. It has been shown that administered amino acids go rapidly into protein anabolism. In attempting to label the parathyroid gland with isotopic amino acids the main theoretical problems were the differential anabolism in the immediate area under analysis, and the relative accretion of the specific amino acid.

The rat parathyroid was labeled with relative selectivity using tritiated methionine as demonstrated by autoradiographic techniques. The parathyroid function was stimulated by a low calcium diet. Thyroid anabolism, which is the most probable source of extraneous emission, was effectively suppressed with thyroxine. The extention of this technique to human begins with hyperparathyroidism is anticipated, using gamma emitting Se_{75}selenomethionine following a high protein diet and thyroxine administration.

The ability to selectively label the parathyroid gland with a high energy emitting radioisotope would be exceedingly helpful in localizing a hyperactive gland either by external scanning or surgical probe counting. There also exists the possibility of ultimately developing a means of physiologic evaluation of parathyroid activity entirely different from any means now available. The development of a method for the in vivo labeling of parathyroid hormone should permit considerable future study of its metabolism and action.

M 1. *"The Uptake of I-131 Labeled Aminoacridine Compounds by Lung Tumors in Rats".* N. B. ACKERMAN, (Minneapolis, Minn.)

M 2. *"Chromatographic Determination of Inorganic 'Unbound' Iodide (I-131 and I-125) in Various Radioiodinated Pharmaceuticals."* HOWARD S. STERN, and HARRY HULIT (Squibb Institute for Medical Research, New Brunswick, New Jersey.)

Many reports have appeared which describe paper chromatographic and electrophoretic methods for radioiodide (I-131), radio-thyroxine (I-131), radio-thyroxine (I-131) analogues, and several other radioiodinated compounds. Investigators employing radioiodinated compounds in clinical and laboratory research studies have been concerned with the percentage of inorganic 'unbound' iodide associated with the preparations. Discrepancies in inorganic iodide assays have often resulted by using different solvent systems for the same compound. Since artefacts may arise during chromatography of high specific activity radioiodide and radioiodinated compounds, depending on the stability of the compound in the solvent system employed, we have attempted to catalogue the best solvent systems used in our laboratory which distinguish between bound and unbound (inorganic) radioiodide and which give reproducible scans from batch to batch.

Inorganic radioiodide (I-131 or I-125) has been spotted concurrently for comparison of standard Rf values to determine solvent stability. Identical results have been uniformly obtained with and without the addition of carrier material at the origin.

Although one-dimensional chromatography has been used throughout the study, many of the compounds have been assayed simultaneously in more than one solvent system with good agreement between inorganic iodide values but with some hetertogeneity evident.

M 3. *"In-vivo Radiophotoluminescent Dosimetry."*[1] C. G. AMATO,[2] S. J. MALSKY,[3] B. ROSWIT,[4] and B. REID[5] (AMF Lab. Industrial Reactor Laboratories, Inc., Plainsboro, New Jersey; U. S. Veterans Administration Hospital, Bronx.)

The ability to measure radiation dose at a site or sites of interest within a patient during therapy or diagnosis is desirable. Such measurements relieve the physician of dependence on idealized mathematical models, and permit him to confirm his treatment plan or modify it on the basis of a measured value. The investigator may implant these miniature dosimeters in animals, cadavers or phantoms in addition to patients.

The system will be described and the steps which must be followed by the user in order to obtain accurate and reliable information will be outlined in detail. Work currently in progress to apply radiophotoluminescent dosimetry to mixed dosimetry will be discussed. Several slides will be shown describing typical clinical applications.

The RPL(1) glass dosimeter is a right cylinder 6 mm high and one mm in diameter. These devices cost approximately $0.44 each. The specifications given in Table I apply to a selected, shielded, low-atomic number dosimeter when read using a realistically determined calibration factor.

Table I

Dosimeter Specifications

Accuracy	±7%
Confidence Limit	99.9%
Range	10r to 20,000r
Directionality(2)	poor

Exposure produces a permanent and cummulative effect so re-use is possible until the upper limit of range is reached.

(1) radiophotoluminescent

(2) Since the dosimeter is not spherically shaped, directionality is poor. This defect is easily overcome by so implanting the dosimeters in a non-isotrophic field so the radiation is normally incident on the longitudinal axis.

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[1]*Work sponsored by the U. S. Veterans Administration, U. S. Atomic Energy Commission, and AMF Atomics.*

[2]*Research Physicist, AMF Atomics, Greenwich, Connecticut.*

[3]*Bronx Veterans Hospital and Dept. of Science and Mathematics, New York University.*

[4]*Chief, Radiotherapy Service, Bronx Veterans Hospital.*

[5]*Bronx Veterans Hospital.*

M 4. *"A Study of Thermoluminescent Dosimetry."*[1] S. J. MALSKY,[2] C. G. AMATO,[3] B. ROSWIT,[4] and C. SPRECKLES[5] (U. S. Veterans Administration Hospital, Bronx; Industrial Reactor Laboratories, Inc., Plainsboro, New Jersey.)

Work is currently in progress to define and to resolve the problems connected with the clinical and experimental application of an in-vivo dosimetry system based on the principle

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[1]*Work sponsored by the U. S. Veterans Administration and The James Picker Foundation.*

[2]*Bronx Veterans Hospital and Dept. of Science and Mathematics, New York University.*

[3]*Research Physicist, AMF Atomics, Greenwich, Connecticut.*

[4]*Chief Radiotherapy Service, Bronx Veterans Hospital.*

[5]*Bronx Veterans Hospital.*

of Thermoluminescence. At this time, these dosimeters are available in the form of right cylincers 10 mm high and 1 mm in diameter; the possibility of reducing length to five or six mils is under study as well as obtaining spherical dosimeters 70 to 80 mils in diameter.

The TL[1] dosimeter's range, as now estimated, covers ten decades of response, 10^{-5} r to 10^{5} r, (0.01 mr to 250,000 r). The application of these dosimeters to nuclear medicine lies, in the opinion of the authors, in the sensitivity of the dosimeters. If low dosage can be accurately measured in-vivo, then these dosimeters will make possible the safe and easy measurement of dose not only in the organ which absorbs the administered radioisotope but also in the surrounding host as well as proximate and remote radiation sensitive organs.

The absorption of ionizing radiation excites the TL phosphor which may be either CaF_2: Mn or LiF. The dosimeter is read by thermally producing blue-green luminescence. The light output is detected with a photomultiplier and converted to a current.

Calibration may be effected by correlating known exposures with either the brightness as indicated by the peak amplitude of a glow curve[2] or the electronically integrated current output. Reading completely erases the signal so the dosimeters are re-usable.

In addition to dimensional and geometric problems, the following factors are under investigation or will be investigated:

1) energy response of the unshielded phosphor;
2) shield design if one is needed;
3) calibration procedures;
4) determination of accuracy, confidence limit, index of precision, range, linearity, directionality, and storage life;
5) implant techniques;
6) applications to nuclear medicine;
7) application to mixed dosimetry.[3]

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[1] Thermoluminescent

[2] A glow curve is a plot of luminescent intensity vs time at a constant heating rate.

[3] The measurement of the gamma dose delivered by a radiation field comprised of gammas and neutrons.

M 5. *"Autoradiographic Demonstration of Thorium Deposition in Tissues."* HENRY LANZ, and LORA SUE KELLER (Radioisotope Service, Veterans Administration Hospital, Dallas.)

This paper is essentially a case report, with short history, of an individual who had received Thorotrast diagnostically nine years prior to this study. Color photomicrographs of liver and spleen sections, with superimposed liquid emulsion autoradiograms will be shown. Histological correlation of the clearly visible Thorium alpha tracks will be pointed out.

M 6. *"Neutron Penetrations in a Phantom Head."* RALPH G. FAIRCHILD (Medical Research Center, Brookhaven National Laboratory, Upton, Long Island.)

The penetration (neutron flux vs distance curve) of a relatively thermal neutron beam was measured in a tissue-equivalent phantom head. The thermalization of the incident beam was varied by changing the thickness of D_2O in its path (Cd ratio of 1/v detector varied between 90 and 180). Penetrations were measured with the incident beam filtered with Cd and Li, and with an unfiltered beam. The epithermal beam resulting when the thermal neutrons were filtered out gave a neutron flux peak at a distance of two to four cm inside the phantom head. Peak flux intensities varied from 1.42×10^{10} n/cm^2-sec to 9.35×10^{10} n/cm^2-sec at a reactor power of 5 MW. The improved neutron penetration of an epithermal beam (surface to peak ratio of approximately four to one, neutron flux remaining above the entrance value in the

region between 0-8 cm) will be useful in neutron capture therapy where it is desirable to deliver a neutron dose at depth without destroying surface tissue.

N 1. *"Pituitary Elimination by Radioactive Implants in Patients with Mammary and Prostatic Carcinoma."* K. SCHEER (Heidelberg, Germany.)

N 2. *"The Proton and Alpha Particle Beam and the Bragg Curve in Medicine"* J. LAWRENCE, C. TOBIAS, J. BORN, L. LINFOOT, A. GOTTSCHALK, and R. KLING, (Berkeley, California)

N 3. *"Clinical Use of Radiocopper (for Early Diagnosis of Wilson's Disease and Schizofrenia)."* P. CZERNIAK (Tel-Hashomer, Israel.)

N 4. *"Use of P-32 and a Miniature Geiger Tube to Detect Malignant Neoplasia of the Gastrointestinal Tract."* ROBERT S. NELSON, WILLIAM C. DEWEY and RAYMOND G. ROSE (The Departments of Medicine and Physics, The University of Texas M.D. Anderson Hospital and Tumor Institute, Houston.)

Radioactive phosphorus (P-32), which sometimes concentrates in cancerous tissue to a greater extent than in normal tissue, has been used to diagnose gastrointestinal neoplasia. Five hundred microcuries of P-32 were administered intravenously to human subjects suspected of having cancer of the esophagus, stomach, or rectum, and 24 hours later the counting rate (about 300-400 counts per minute) was determined with a small geiger counter (sensitive area 5 × 10 mm) placed in direct apposition to the mucosa of these organs. In the esophagus and rectum, the counter was placed in the tip of a relatively rigid plastic tube, which was then inserted through the esophagoscope and sigmoidoscope. A controllable-tip gastroscope fitted with the counter just distal to the lighting unit was used to evaluate the stomach under direct vision. A malignant area usually counted from 30% to twice higher than an adjacent normal area. In 45 esophageal tests (22 with malignant tumors) there were two false negatives and two false positives. Seven of 24 gastric tests were unsatisfactory because of inability to pass the cardia or to reach the tumor (an instrument defect now rectified); of the 17 remaining (three with malignant tumors) there were one false positive and two false negatives. All of four rectal tests (two with tumors) were correct. Further improvements in geiger counter probe equipment, now under development, may increase accuracy. While the use of radioactive phosphorus in the evaluation of malignant gastrointestinal neoplasia probably is not feasible as a survey method, preliminary tests show promise in the differentiation of obscure lesions, especially in the esophagus, and it may be a means of discovering cancer not obvious on routine examination.

O 1. *"The Pulmonary Circulation Time and Radiocardiographic Pattern in Bilharzial Cor Pulmonale."* MUHAMMAD ABDEL RAZZAK (Cairo University and A.E.E., U.A.R.)

Cardio-pulmonary schistosomiasis (bilharziasis) is characterized by widespread narrowing or obliteration of the pre-capillary vessels with little or no involvement of lung parenchyma. This vaso-occlusive process results from widespread recurrent embolisation with bilharzia ova, and leads to progressive rise in pulmonary artery pressure, which consequently causes right ventricular strain and gross dilatation of the pulmonary arterial tree.

An easy and accurate method to study the effects of this obliterative pulmonary endarteritis on the heart and on the velovity of blood flow in the lesser circulation is by radiocardiography using RISA.

This report deals with the findings in 33 patients having bilharzial cor pulmonale and representing the three different grades of this disease. The obtained results indicate that there is a close correlation between the radiocardiographic pattern, pulmonary circulation times (PCT) and the clinico-radiologic grades of bilharzial cor pulmonale. In grade I, both PCT and radiocardiogram were normal. On the other hand, radiocardiography in grade II revealed moderate prolongation of the descending limb of R wave and PCT. Grade III was characterized by marked increase in the duration of PCT, together with a huge R in the radiocardiogram due to prolongation of both ascending and descending limbs of this wave.

O 2. *"Red Cell Survival in Primary and Metastatic Cancer."* FRANZ K. BAUER, JOSEPH Z. WALKER, and JUANITA LESTINA (Medical Service, Los Angeles County Harbor General Hospital, Torrance.)

Although it is known that patients with cancer develop anemia, little is known about the mechanism of this anemia. A hemolytic factor in cancer has been postulated. This was based on the fact that red cells from normal donors have a shortened survival when injected into patients with cancer, whereas red cells of cancer patients have a normal survival time when injected into normal patients.

The present study was undertaken to find out whether red cell survival is shortened in patients with primary and curable cancer, or whether shortened red cell survival is peculiar to metastatic cancer only. Patients with a preoperative diagnosis of cancer of the breast were studied, as well as patients with suspected lung cancer. None of them had anemia. Operative findings and a 2½ year survival constitute the basis for this report. Red cell survival in control patients without anemia or cancer was 35 days. Patients with Broders stage 1 and 2 breast cancer showed normal survival times whereas those with stage 3 and 4 had statistically significant shortening of the survival times. Patients with primary cancer of the lung had a survival half time of 30 days whereas those with metastases had a mean survival time of 27 days. Statistical analysis showed these differences to be significant. In chronic noncancerous pulmonary disease, the mean survival was 35 days, the same as that of the control group.

These preliminary observations indicate that red cell survival is shortened only when the primary cancer has spread beyond its original site. Whether this method can be used to exclude metastatic involvement remains to be demonstrated by more extensive work.

O 3. *"The Simultaneous Use of Fe^{59}, Cr^{51}, and Co^{57} in the Study of the Erythrokinetics of the Postgastrectomy State."* DON R. SANTCHI, W. NEWLON TAUXE, and HAROLD H. SCUDAMORE (Mayo Clinic and Mayo Foundation, Rochester, Minnesota.)

In an attempt to delineate the various etiologic factors in the anemia that often follows gastric surgical procedures, both orally and intravenously administered isotopes—Fe^{59}, Cr^{51}, and Co^{57}—were used in the study of 27 subjects who had had partial gastrectomy (25), total gastrectomy (1), or gastrojejunostomy (1). In particular, measurements were made of the rates of destruction of red blood cells, turnover of iron in plasma and marrow, loss of fecal blood over a 10-day period, absorption of orally administered iron and vitamin B_{12}, and fecal excretion of fat. It is concluded that: (1) the anemia following gastric surgery is due to one or more of a number of factors; (2) none of the various factors can be considered to be the one fundamental cause of the anemia; (3) abnormal gastrointestinal loss of blood occurs in these cases (even in the absence of historical clues to, or routine laboratory confirmation of, its existence) and can significantly contribute to the degree of anemia present; (4) increased absorption of iron can be demonstrated in postgastrectomy subjects; (5) a recently described method of testing the absorption of orally administered iron appears to be an advance in the

study of normal and abnormal gastrointestinal absorption of iron; and (6) the use of a combined-administration, multiple-isotope technic is of significant advantage in the investigation of the erythrokinetic abnormalities that can occur in the postgastrectomy state.

O 4. *"Lanthanum-140 as a Measure of the Completeness of Stool Collections for the Oral Iron-59 Absorption Test."* R. L. Hayes, Bill M. Nelson, J. E. Carlton (Oak Ridge Institute of Nuclear Studies, Oak Ridge.)

Tests of a patient's ability to absorb certain orally administered materials may be invalidated by incomplete collection of feces. La^{140} with an appropriate carrier is not appreciably absorbed from the gastrointestinal tract and may be given orally simultaneously with another tracer. Practically all of the La^{140} is accounted for in the feces if collections are complete. To date, seventeen persons have been given La^{140} (20 microcuries with 5 milligrams stable lanthanum) with Fe^{59} (2 microcuries and 50 micrograms) as an oral iron absorption test. The test was considered satisfactory in that the iron absorption could be correlated with the clinical state. Surprisingly, a small but significant amount of Fe^{59} continued to appear in late stool specimens after virtually all of the La^{140} had been recovered. Generally this Fe^{59} was less than 5% of the dose and was not clinically important for the iron absorption test, but was too large to be accounted for by fecal loss of Fe^{59}-labeled red cells. However, in one test 100% of the La^{140} had been collected in the first three days but subsequent stools had 23% of the Fe^{59} dose. It had been expected that the fecal Fe^{59} and La^{140} activities would have a constant relationship so that a correction factor could be applied if collections were incomplete. However, because of the prolonged excretion of Fe^{59}, the ratio of Fe^{59} to La^{140} rises with each stool collected. The prolonged excretion may be due to transient binding of the iron to the mucosa of the digestive tract but this remains a speculation.

O 5. *"Total Iron-Binding Capacity in Normal Pregnancy."* George D. Malkasian, Jr., W. Newlon Tauxe, and Albert B. Hagerdorn (Mayo Clinic, Rochester, Minnesota.)

Employing radioactive iron, we have determined the total iron-binding capacity in normal pregnant women who (1) had received no iron therapy, or (2) had received oral ferrous sulfate as supplementary treatment for 2 or more months. Similar determinations were made on blood (3) from the umbilical cords of infants and (4) from women in the postpartum period. The serum iron levels remained within normal levels throughout pregnancy and the postpartum period. The total iron-binding capacity rose above normal non-pregnant levels in the sixth lunar month of pregnancy among group 1, and in the seventh lunar month among group 2. In both, it tended to fall toward normal in the month prior to delivery. The total iron-binding capacity had returned to normal by the end of the third postpartum week. The serum iron level of cord blood was consistently higher than maternal levels despite the total iron-binding capacity's being consistently lower than maternal levels.

O 6. *"Physiological Effects of Erythrocytic Factors in Dogs. Part I: Effect on Blood Volume and Red Blood Cell Regeneration."* Marvin Berg (Marymount Hospital, Garfield Hts., Ohio.)

Although much has been published concerning plasma factors which affect erythropoiesis, the literature is meager concerning erythryocytic factors.

Factors derived from oanine erythrocytes were administered to dogs and blood volumes were done using RISA, Fe-59 and Cr-51. Alterations in the rate of red cell regeneration following a bleeding stress were also studied.

Erythrocytic factors were prepared from saline washed and from unwashed red cells. Both washed and unwashed cells were hemolysed with sterile distilled water (2 parts cells plus 3 parts water) and then made isotonic by the addition of an appropriate amount of 20 per cent sodium chloride.

A blood volume increasing factor (unwashed red cell hemolysate) was found which elevated the blood volumes of recipient dogs, the increases ranging from 20 to 200 per cent. The blood volume decreasing factor (washed red cell hemolysate) lowered the circulating blood volumes by as much as 45 per cent. Since the blood volume changes were transient, usually returning to their normal values within forty-eight hours, it was felt that a non-circulating volume of blood existed which is not measurable by any of the existing methods for determining circulating blood volumes.

Dogs bled of 40 per cent of their measurable blood volumes and administered an erythrocytic factor (unwashed red cell hemolysate), showed a more rapid rate of regeneration of their red cell mass than did the bled controls, reducing the time for a return to normal from 26 to 11 days.

Evidence was found to support a concept that erythrocytic factors, in combination with plasma factors, promote a more rapid regeneration rate for red cells.

P 1. *"Individual Renal Plasma Flow (Quantitative Methods with Radiohippuran)"* EARL K. DORE, GEORGE V. TAPLIN, DELORES E. JOHNSON, HARRIET S. KAPLAN (Laboratory of Nuclear Medicine and Radiation Biology, UCLA Medical School, Los Angeles; Department of Radiology, Los Angeles County Harbor General Hospital, Torrance.)

None of the numerous attempts to quantitate the renogram as an indicator of individual renal blood flow or function, are entirely satisfactory because of misinterpretation of the tracings. The renogram's second segments are indices of individual renal plasma flow because hippuran is retained in the kidney during this period and tracer doses are extracted with high efficiency. The flow to each kidney may be calculated from the ratio of the blood flow slopes of the renogram (tangents) provided one knows the flow to both kidneys, or the clearance of hippuran. The hippuran clearance following continuous I.V. infusion gives the effective renal plasma flow (ERPF). If the infusion is made with a motor driven syringe and equilibrium between the rates of infusion and excretion are registered (heart detector) there is no need for urine collection

$$\text{ERPF in ml/min} = \frac{\text{I.V}}{\text{P}} = \frac{\text{c/ml infusate x ml/ min infused}}{\text{c/ml plasma}}$$

Thus, if one knows total flow T from the ERPF and the ratio of blood flow slopes between kidneys, r, the flow to each kidney may be calculated from the formula

$$L_t = \frac{1}{r+1} T \text{ and } R_t = \frac{r}{r+1} T, \text{ where L} = \frac{\text{the kidney with the lower}}{\text{blood flow slope}}$$

A possibility for further simplification is to substitute for 15 minute hippuran excretion value at the end of the renogram for ERPF. Preliminary data indicate good correlation. Results of comparative studies in normal subjects and patients with renal disease will be presented.

P 2. *"Principles of Rates in Relation to the Renogram and Thyroid Uptake."* SOL TAPLITS (Jewish Hospital, Cincinnati.)

The methods used in the performance of the renogram violate the fundamental principles of rates. When recording the components of a curve that represent functions of the target organ, counts rather than percentage against time are registered. Counts per se do not represent function but may represent variables unrelated to the target organ. The first principle that one must observe is that the ratio of counts to dose must be recorded,—more explicitly, percentage. The second principle is that the rate or slope of any curve is proportional to the dose. It is therefore evident that any dose given in accordance with body weight will violate the second principle and the slope will vary with change of dose rather than with change of function. This violation would be similar to that of performing a 24 hour uptake study of the thyroid without reference to the dose as a standard equal to 100%. Methods will be described how to record percentage directly with the ratemeter. Also, a method will be demonstrated wherein the dose will not affect the slope so that the changes in rate will be solely as the result of change in function of a target organ or gland.

By utilizing these principles, a unique method of recording functions of both kidneys simultaneously by means of one detector, ratemeter, spectrometer, and recorder has been developed, thus obtaining two curves. The method can be used universally with any instrument that is available.

P 3. *"Detection of Unilateral Renal Disease by Measurement of the Rate of Uptake of Hg-203 Chlormerodrin."* RICHARD C. REBA, JOHN G. MCAFEE, and HENRY N. WAGNER, JR. (Division of Nuclear Medicine, The Johns Hopkins Medical Institutions, Baltimore.)

In a group of 147 hypertensive patients and in 17 selected normal individuals the rate of accumulation of Hg-203 chlormerodrin was measured and evaluated as a practical test of individual renal function for screening large numbers of hypertensive patients. The accumulation rate of the radiomercurial for each kidney was recorded using paired external scintillation detectors during a 30-60 minute period. The results were expressed as a ratio of the count rate at any time t, to the count rate at five minutes following an intravenous injection (Ct/C5). The Ct/C5 ratios of the right kidney were then divided by the corresponding ratios of the left. These right/left ratios proved to have a well defined normal range.

In 30 out of 31 patients with unilateral renal disease, associated with hypertension the values fell outside the normal range. The results in 116 patients with hypertension not associated with unilateral renal disease did not statistically differ from the group of normotensive individuals. This ratio proved to be a reliable criterion by which the function of one kidney could be compared with the other. Scintillation scanning of the kidneys did not always detect the presence of unilateral renal lesions; its contribution lay in its ability to demonstrate differences in renal size, segmental areas of ischemia and infarcts.

The results of the chlormerodrin uptake will be compared with the I-131 Hippuran Renogram, intravenous pyelograms, renal arteriograms, and bilateral ureteral catheterization studies.

P 4. *"The Value of the Renogram in Following Patients through Pelvic or Abdominal Irradiation."* JEROLD GREEN, ROBERT BRUNEAU, PHILIP RUBIN (Radiation Therapy and Nuclear Medicine, Strong Memorial Hospital, Rochester, New York.)

Sixty patients undergoing pelvic irradiation were subject to radio renogram study prior to the onset of radiotherapy. Subsequent studies were performed at varying intervals both during and after the course of therapy. The group included patients with lymphoma and gynecological and urological malignancies. The renogram was found to be of value from the following points of view: 1) documenting decreased renal function or obstruction prior to the onset of irradiation. (2) determining the efficacy of radiotherapy in reversing complete or partial ureteral obstruction secondary to tumor. (3) observation of progressive urinary tract obstruction, as a guide to the necessity of a urinary diversion procedure. (4) subsequent patient follow-up. (5) as a rapid method of detecting clinically unsuspected renal and/or ureteral involvement in retroperitoneal disease processes.

The renogram is an economical and rapid screening procedure which has become an essential part of our routine care of the patient undergoing pelvic or abdominal radiotherapy. Intravenous pyelograms were obtained prior to irradiation and in those instances where the renogram indicated a subsequent abnormality. The correlation between the two studies will be discussed.

P 5. *"Renograms and Cardiac Studies with a Single Probe."* D. L. TABERN, and LIELA HALPERIN (Highland Park Hospital, Lake Bluff, Illinois.)

A study was made of the practical factors which, in many institutions, still cause the Renogram to be looked upon with some suspicion. The obvious conclusion was that the

accuracy and readability of the Renogram curves are directly related to instrumentation. With proper shielding and spectrometry, the larger the crystal, and the wider the collimation, and the greater the number of counts /min secured, the more accurate the determination.

With the inclusion of the Hg 203 Neohydrin Renal Scan as a routine part of the kidney workup, it was soon found that such a scan provided the answer in many questionable cases. On occasion, it established that the overall relative functions of the two organs as indicated on the Renogram were actually incorrect. The ability to see space occupying lesions and locate the exact area of decreased function is highly important at arriving at a proper diagnosis.

A technique was then developed, employing the Magnascanner as the sole instrument required for the Hippuran Renogram, the Neohydrin Renogram and the Renal Scan. Briefly the 3x2 probe, being mounted on a readily moved beam, is positioned, for either 30 or 60 second intervals over each kidney in turn. At the high counting rates secured with this system, either time is ample for securing stable readings. These values are subsequently plotted. Phantom studies established that an area the size of the kidney could easily be covered with an accuracy of 90%, and that the background from the second kidney was less than with many standard systems. Numerous clinical cases studied consecutively, or simultaneously, by the standard, and the proposed method, have shown that the function curves are essentially identical.

It is felt that in those instances where both a large crystal dual probe system, and a scanner are not available. The highly valuable information supplied by the scan far outbalances the slightly greater personal effort required for the method described.

P 6. *"A Diagnostic Score Useful for Evaluating the Renogram of Hypertensive Patients."* PHILIP C. JOHNSON and DWIGHT D. ODOM (Department of Medicine, Baylor University College of Medicine, Houston.)

Hippuran I-131 renograms were analyzed on 129 consecutive hypertensive patients (mean age 62 years) hospitalized during a 6 month period, each of whom received an aortogram, split function studies and surgical correction of all vascular lesions. The time to peak concentration, the time to 75% and 50% of peak concentration, the angle the concentration curve makes with the ordinate, curve height, presence of a prominent vascular phase and failure of the curve to reach 50% concentration in 20 minutes were analyzed. Borderline abnormalities were confirmed by repeating the curve during dehydration or water loading. The ratios (left/right) obtained from these curves showed the following ranges.

	Peak	75%	50%	Ht.	Angle
Normal Ratio	0.8-1.2	0.8-1.2	0.8-1.2	0.7-1.3	0.6-1.4
Normal Range	1.5-5.5	3.1-8.7	15.0-2.0		9.0-57.

Three or more ratios outside of the normal limits was used to indicate significant disease. Water loading generally decreased the number of abnormal values by one, whereas dehydration increased it by one. Post operative renograms, as early as one week, have shown a decrease in the number of abnormal ratios.

Using the criteria of 3 or more abnormalties, the percentage of false negatives were 7.6% and false positives were 2.7 and 89.6% correct interpretations. As a comparison, intravenous pyelograms of these patients produced 27% false negatives and only 73% correct diagnosis. These results show that the renogram is capable of giving correct information concerning the presence of renovascular lesions in most hypertensive patients.

P 7. *"Experience with Determination of Blood Volume in a General Hospital."* MENARD IHNEN, and DOROTHY KELSEY (Augusta, Georgia.)

Experience obtained from estimation of total blood volume of 188 patients in a general hospital has been reviewed. Determining red cell mass and estimating total blood volume has

offered no significant technical difficulties. It has been practical to offer this service from a busy laboratory in a general hospital. Utilization has been erractic. Surgical patients with anemia, pre-operative patients who are questionable risks or who are to have extensive procedures, post-operative patients who do not respond as expected, patients with vasomotor instability, and patients with suspected polycythemia vera have been the most frequent subjects. Review of hospital records reveals that blood volume values were quite frequently either significantly greater or less than expected. It was apparent that estimation from clinical signs and symptoms was not adequate. There is a considerable tendency to assume that concentration measurements (hemoglobin and packed cell volume determinations) can be used to judge total blood volume; review of the cases demonstrates the fallacy of this assumption and the need for more frequent determination of the blood volume in clinical practice. Multiple determinations were made in a small number of patients before and after transfusion therapy. A quantitative increase in blood volume for several hours was found and elevated levels continued for a day or more. The type of transfusion therapy was frequently influenced by the values for plasma volume or red cell mass.

Q 1. *"A Clinical Test Useful in the Determination of Portal Hypertension."* RALPH D. EICHHORN, SAMUEL SIMKIN, and PHILIP C. JOHNSON (Department of Medicine, Baylor University College of Medicine, Houston.)

The diagnosis of portal hypertension remains a problem in clinical medicine, Anatomical considerations have suggested that in the presence of portal hypertension, blood entering the superior hemorrhoidal vein will pass through the internal iliac vessels rather than take the normal course via the portal vein. Through an anoscope, we have injected 40 uc iodopyracet I-131 submucosally in the general area of the superior hemorrhoidal plexus to determine the direction of flow in the superior hemorrhoidal veins. Placing a detector over the heart and another over the liver connected to ratemeters and a dual channel recorder, we find that iodopyracet reaches the liver first in normals and the heart first in patients with portal hypertension. The difference in heart to liver arrival time of patients with portal hypertension ranged from 1 to 50 seconds.

Using this procedure in 30 patients, we have found a clear separation between patients with portal hypertension and patients without liver disease. This method is technically simple and can be used as a routine diagnostic test in patients suspected of having portal hypertension.

Q 2. *"Measurement of Forearm Blood Flow in Man with Radioactive Krypton and Xenon."* GERALD B. HOLZMAN, HENRY N. WAGNER, JR., MASAHIRO IIO, DAVID RABINOWITZ, and KENNETH L. ZIERLER (The Johns Hopkins Medical Institutions, Baltimore.)

If the rate of removal from the site of injection of an intramuscularly injected tracer is limited principally by blood flow, then clearance of the tracer from the injection site can be used to measure blood flow. This principle, proposed in 1945, was applied to the clearance of Na-24; however, results with Na-24 have been variable. Because a large portion of this variability could be due to a limitation on clearance rate by the process of diffusion, experiments were designed using Kr-85 and Xe-133, which diffuse out of (and, therefore, back into) capillaries much more readily than sodium. Clearance of aqueous solutions of these inert gases was measured 107 times in 43 persons. Regardless of the detection system or volume of injectate used, clearance was not a single exponential function; nevertheless, the initial decrease in log of radioactivity was sufficiently linear to permit estimation of flow. For our purposes, half-time was defined as time required for counting rate to fall to one-half the value obtained 2½ minutes after injection. The krypton-85 half-time was 17.6 ± 11.3 min. (mean ± S.D.), yielding a forearm muscle blood flow of 3.9 ml./100 g./min. The mean difference between two observations in the same subject was 28 per cent. That blood flow was a major determinant of clearance was indicated by the findings that arterial occlusion completely abolished clearance of radioactivity, that during venous occlusion average flow was

reduced by 75 per cent, and that reactive hyperemia produced a marked increase in clearance. That factors other than blood flow influenced clearance rate was indicated by the finding that Xe-133 was cleared faster than Kr-85 when both were injected simultaneously. Studies comparing the clearance method to simultaneous measurements of blood flow by the dye dilution technique are in progress.

Q 3. *"Radioactive Krypton and Xenon in the Measurement of Coronary, Hepatic, and Cerebral Blood Flow."* MASAHIRO IIO, HENRY N. WAGNER, JR., RICHARD S. ROSE, KEIJI UEDA, PAUL R. LICHTLEN, JAMES R. JUDE, G. GUY KNICKERBOCKER, and HENRY R. BOURNE, JR. (The Johns Hopkins Medical Institutions, Baltimore.)

Barger and his associates injected aqueous solutions of radioactive krypton into the coronary artery of dogs and measured the rate clearance of the radioactivity from the heart by means of an external scintillation detector. (Am. J. Physiol. 203, 122, 1962) Since the clearance of this lipid-soluble, physiologically inert substance is limited primarily by blood flow, measurement of the clearance rate can be used to determine coronary blood flow. Our initial experiments confirmed the good agreement between this method and simultaneous rotameter measurements in 10 dogs whose coronary flow was varied with drugs. In six other dogs, Kr-85 solutions were injected into the left anterior descending coronary artery through a cardiac catheter; in these anesthetized, but otherwise normal dogs, the half-time of the exponential decrease in radioactivity over the precordium averaged 0.55 minutes (range: 0.33 to 0.88). Using similar principles, hepatic blood flow was determined by injecting Kr-85 and Xe-133 solutions into the splenic vein of 13 dogs. Similar results were obtained with percutaneous injection of the spleen itself. When recorded by an external detector over the liver, the clearance half-time in 61 experiments averaged 0.46 minutes (range: 0.30 to 0.77). A close correlation was obtained when this method was compared to simultaneous measurement of hepatic blood flow by the colloidal gold (Au-198) clearance technique during periods of graded portal vein occlusion. To obtain cerebral blood flow, solutions of the radioactive gases were injected into the internal carotid artery of nine dogs. The half-time of clearance measured with an external detector over the skull averaged 0.96 minutes (range: 0.58 to 1.53 in 34 experiments). During ventricular fibrillation, clearance was abolished; external cardiac massage during fibrillation returned cerebral blood flow to 11 to 42 per cent of control values. Subsequent defibrillation returned the clearance rate to nearly normal values. These studies indicate the usefulness of this new method of measuring regional blood flow. Data comparing Kr-85 with Xe-133 will be presented.

Q 4. *"Clinical Measurement of Brain Permeability to Gamma-emitting Labeled Compounds."* W. H. OLDENDORF, M. KITANO (Wadsworth General Hospital, Veterans Administration Center; Department of Medicine, University of California, Los Angeles.)

Using a pair of large crystals and suitable collimation, a gamma detection system has been constructed with the intention of uniformly monitoring the entire cranium rostral of the floor of the cranial cavity. The radioisotope to be measured is administered intravenously in a dosage of 0.1 microcurie per kilogram and the total cranial content is measured at 1 minute intervals. At 2 minutes antecubital venous blood samples are begun, and the blood fall off is followed until the blood level is out of the range of measurement. It is assumed that at 2 minutes the entire cranial content of the material is in the blood of the brain. With this as a baseline the brain blood content is subtracted from the total brain content, leaving the brain tissue content. This is a function of the mean brain capillary permeability to the labeled compound and its rate of blood fall-off.

Several of the commonly available labeled compounds have been studied. These have included I^{131} hippuran, rose bengal, and serum albumin. With Hg^{203} labeled neohydrin the brain tissue fall-off curve in a series of 20 patients, which contained 10 tumors, shows a high degree

of correlation with pathology. The significance of this approach is the extremely small dose of isotope which the relatively uncollimated detectors allow because of their very favorable geometry. The possibility of utilizing metabolically active labeled gamma-emitters will be discussed.

Q 5. *"The Elasticity of the Cranial Blood Pool."* M. KITANO, and W. H. OLDENDORF (Wadsworth General Hospital, Veterans Administration Center, and Department of Medicine, University of California, Los Angeles.)

Normally the cranial cavity contains 150 to 200 cc. of blood, largely on the venous side of the capillary bed of the brain. The cranial blood pool is not very elastic but the rise in intracranial pressure which results from jugular venous compression is clear evidence that the pool is capable of a certain degree of stretching. The increase in volume is limited by the elasticity of the dura, particularly of the spinal dura, since the cranial cavity is rigid and only slight expansion is possible at the various foraminae.

This study utilizes a dose of intravenously administered serum albumin. A detector uniformly sensitive to the entire cranial cavity counts the amount of radioisotope contained in the cranium. It is assumed that for the first hour this will, with serum albumin, be entirely within the cranial blood pool. A blood pressure cuff is placed about the neck and inflated in graduated steps to 60 mm. of mercury. The change in cranial blood volume as a function of neck venous compression is measured. The patient suffers little discomfort.

Experiences attempting to measure cerebral blood flow by this plethysmographic technique will be described. With pressures under 50 mm. of mercury, the cranial blood pool expands 10 to 30% in volume.

Q 6. *"Observations of Cerebral Arterio-Venous Transit Time Using Radio Iodinated Human Serum Albumin.* ROBERT L. BELL (Section of Neurological Surgery, U. S. Veterans Administration Hospital, Consolidated Center, Wadsworth, Kansas.)

During the past year it has been possible to improve accuracy in the measurement of cerebral arterio-venous I^{131} transit times. This improvement has been accomplished by better shielding and placement of the detectors, the introduction of dual precision rate meters, and a higher quality tape recording system. In addition, we have developed the data instantaneously by a dry process using an oscillograph with a wide range of speeds and time markings. This latter feature permits instantaneous evaluation of data and adjustment of the circuitry to enhance various portions of the record. The tracings are easily obtained from serial angiography. This study includes fifteen patients who have been subjected to this improved technique. Accurate evaluation of the transit time was possible in each instance.

Q 7. *"Sr^{90} Metabolism in Man During Low Sr^{90} Intake."* HERTA SPENCER, JOSEPH SAMACHSON, EDWARD P. HARDY, and JOSEPH RIVERA (Metabolic Section, Veterans Administration Hospital, Hines, Illinois; U.S. Atomic Energy Commission, New York Operations Office, New York.)

Sr^{90} balances were performed during low Sr^{90} intake of an average of 3.3 $\mu\mu$c/day on 10 young volunteers under strictly controlled metabolic and dietary conditions. Balances of Sr^{90} and Ca were determined on aliquots of 6-day collections of urine and stool, and on aliquots of the diet. No radioisotope was given. Sr^{90} in the diet, urine and stool were determined by low-level counting. An average of 2.9 $\mu\mu$c or 88% of the ingested Sr^{90} was passed in stool. The average urinary Sr^{90} excretion was 0.42 $\mu\mu$c/day corresponding to 12% of the Sr^{90} intake. The Sr^{90} balances ranged from -1.3 to $+1.1$ $\mu\mu$c/day and the average balance of all persons studied was zero. The absorption of calcium was higher than of Sr^{90} and the Ca/Sr^{90} absorption ratio of the 10 volunteers averaged 2.2. The balance data obtained in this study will be

compared to those of 12 volunteers of a similar age group on whom Sr^{90} and calcium balances were measured during a relatively high Sr^{90} intake.

Q 8. *"A Study of the Uptake of T-3 by Dry Resin."* WALTER DIGIULIO, PAUL WEINHOLD, and GEORGE THOMA (Section of Nuclear Medicine, Department of Medicine, St. Louis University School of Medicine, St. Louis.)

A study of the factors which influence the sensitivity and variability of a test which measure T_3 uptake by resin has been made. Dried resin can be simply and rapidly dispensed for use in this test, but aberrant results will occur when drying is excessive or when resin is allowed to reabsorb variable amounts of moisture. In addition, variations in resin particle size will affect the uptake efficiency per unit weight of resin. When these factors are acknowledged and controlled, large numbers of vials containing resin and tris buffer can be prepared and can be expected to have highly uniform uptake efficiency.

Variations in purity of T_3 shipments cause unavoidable fluctuation of T_3 uptakes, but each shipment can be depended upon to give uniform results for at least two weeks.

The sensitivity of the test is a function of the level of the per cent uptake by pooled normal serum. When normal pooled serum uptakes fall near the extremes (0 or 100%) the spread between normal and abnormal values is diminished. This occurs regardless of the methods employed in measuring the uptake.

Over 3400 tests on pooled serum and 300 tests in duplicate on 270 patients were performed. Males and post-menopausal females had normal values that were lower than those for pre-menopausal females. There was good discrimination between normal and abnormal groups.

Q 9. *"Screening of Unselected Hypertensive Patients with Radiorenography."* ROBERT A. NORDYKE and A. MARIA BRAULT (Straub Clinic, Honolulu.)

Radiorenography has reached a state of simplicity and reliability which makes it applicable to the screening of large numbers of hypertensive patients. It is far simpler than any other current procedure for separating out patients who may have surgically curable kidney lesions from the total hypertensive population. This report presents the first part of a continuing study designed to determine the usefulness of obtaining a radioisotope renogram on every hypertensive patient without regard to age, history, signs or symptoms.

Five hundred consecutive hypertensive patients seen at Straub Clinic, a large private medical group, were screened by radiorenography between January and August, 1962. The only criterion for inclusion in the study was a diastolic blood pressure of 90 mm Hg on two or more occasions. All patients referred for a special hypertensive workup were excluded. Patients with normal renograms were not studied further.

Seventy-seven (15.4 per cent) of the 500 showed left-right differences on the renogram. Of these, 66 had IVP's (76 per cent abnormal), 23 had aortograms (83 per cent abnormal). Despite incomplete followup of abnormal renograms by more definitive procedures, 24 patients (4.8 per cent) were found with renal lesions amenable to surgery. These included 11 instances of renal artery obstruction, and a variety of other lesions such as cysts, infarction, hydronephrosis and unilateral contracted kidneys. Sixteen have had operative procedures to date: 12 now have reduced blood pressure levels or are normotensive.

Of special interest are four patients with abnormal renograms but normal IVP's who had aortograms: three of the four aortograms were abnormal, two had surgery and both have improved blood pressure levels.

Although false negative results may occur, it seems likely that many serious renal lesions will be detected by this method which would be missed by more cumbersome techniques applied selectively. Screening by radiorenography will probably uncover curable renal lesions in well over 5 per cent of unselected hyptertensive patients.

R 1. *"C^{14} Tripalmitin Disappearance Curves in the Human."* L. FEINBERG, H. SANDBERG, L. SEMANA, S. BELLET, A. RUTTENBERG and S. MILKE, (Philadelphia, Pa.)

R 2. *"Metabolic Fate of I^{131}-Antipyrine. A Clinical Study."*[1] E. R. Gabrieli, T. Pyzikiewicz, and M. A. Sullivan (Research Division of Clinical Laboratories, State University of New York at Buffalo, Buffalo.)

Catabolism of antipyrine presumably involves oxydation to 4-hydroxy-antipyrine and subsequent conjugation with glucuronic acid. Both these catabolic steps take place within the liver cells. Since radioiodinated antipyrine (RIAP) is tagged right at the fourth carbon position, its hydroxylation and conjugation should be preceded by deiodination. We investigated the fate of RIAP with the hope that its catabolic kinetics might reflect abnormalities of hepatic function in various liver diseases.

To block the thyroidal uptake of iodine released from RIAP, patients were prepared with Lugol's solution for two days. RIAP was injected intravenously and the radioactivity content was followed in the blood and urine. In order to separate the antipyrine-bound radioactivity from the liberated tag, samples were passed through a Dowex-3 anion exchange column. RIAP could be readily eluted with weak acetic acid, whereas the liberated tag was retained quantitatively in the column.

In the blood, a precipitous drop in radioactivity occurred during the first five minutes, signifying rapid equilibration of RIAP within the antipyrine space. This was followed by a second, much slower decrease, interpreted as reflecting the catabolic phase. During this phase a rapidly increasing portion of the plasma radioactivity was due to the released I^{131} tag. In the urine, an insignificant amount of radioactivity was found during the first hour, indicating no renal loss of RIAP. Soon thereafter, a rapid excretion of radioactivity was noted. Chromatography of the urine samples showed an increasing portion of the radioactivity to be the liberated tag.

Liver impairment strikingly affected the kinetics of RIAP catabolism. The impaired ability of the liver to liberate the tag could be readily quantitated by the described procedures. With some simplifications, this test could become not only a valuable, but also a practical clinical liver function test.

R 3. *"Studies of Tooth Movement Using Calcium-45 in Dogs."* Alfred Juda, Jerome Sklaroff, D. Walter Cohen, and Joseph L. Rabinowitz (Radioisotope Service, Veterans Administration Hospital; Department of Periodontology, University of Pennsylvania Dental School, Philadelphia.)

The purpose of this study was to evaluate the calcified tissue changes during orthodontic tooth movement in the dog. A spring wire was used to cause the tooth motion and the animals were given 1 millicurie of calcium-45 intramuscularly and 1 Gm of tetracycline prior to sacrifice. Microroentgenograms, microautography, histological sectioning and fluorospectrometry (from the tetracycline) were used in the evaluation of the results. Previous results indicate that teeth under physiological stress produce less tissue damage than those under excessive stress and, accordingly, move more rapidly. By these techniques it was possible to observe the actual degrees of absorption, reabsorption and deposition in a given time period. Bone formation was observed in both the pressure and tension sites during movement with heavy forces. Osteoblasts were found on the tension site and both osteoblasts and osteoclasts on the pressure site. New calcium deposits were found in the pulp chambers of the moved teeth as well as the control teeth.

R 4. *"Use of Radioactive Vitamin B_{12} to Measure the Glomerular Filtration Rate (GFR)."* Wil B. Nelp and H. N. Wagner, Jr. (Division of Nuclear Medicine, University of Washington, Seattle; and Johns Hopkins University, Baltimore.)

A substance excreted by glomerular filtration and labeled with a gamma-emitting radio-

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[1]Supported by Grants GM-10609-01 and AI-05271-01 from the National Institutes of Health.

isotope would permit a rapid and simple method for measuring the GFR. Based on observations that free (non-protein bound) stable vitamin B_{12} and inulin clearances were similar (Watkin), the mechanism of vitamin B_{12} excretion was studied to determine if radioactive vitamin B_{12} clearance would provide a measurement of the GFR.

A lack of tubular secretion of free vitamin B_{12} was established in the aglomerular toadfish. Total body counting of fish injected with 2000 μg of radiovitamin revealed 94% was retained after 38 days. Stop-flow studies in dogs during simultaneous inulin and Co^{57} vitamin B_{12} infusions indicated vitamin B_{12} was not secreted *or* reabsorbed in the renal tubules. In patients the simultaneous clearances of free Co^{57} vitamin B_{12} and inulin were nearly identical. In 25 collection periods the ratio of C_{free} B_{12} to C_{inulin} was 0.99 ± 0.07 (mean ± 1 S.D.). Protein binding of the infused radiovitamin was negligible when the binding sites were pre-saturated with stable vitamin B_{12}. Thus, clearance was readily determined by measuring total plasma radioactivity.

These results support the concept that free vitamin B_{12} is excreted only by glomerular filtration. In addition to rapid measurement of the GFR, continuous monitoring of GFR or differential study of filtration by external detectors should be possible using radioactive vitamin B_{12}.

R 5. *"Cr-51 Albumin Studies of Gastro-Intestinal Protein Loss in Patients with Malabsorbtive Disorders."* R. SCHAPIRO and W. MACINTYRE, (Cleveland, Ohio.)

R 6. *"The Competitive Effect of Varying Particle Sizes on the Clearance of Colloidal Material by the Reticuloendothelial System."*[1] ROLF L. SCHAPIRO and WILLIAM J. MACINTYRE (Department of Medicine, Western Reserve University, Cleveland.)

In order to determine the effect of particle size on the phagocytic mechanism of those reticuloendothelial elements known to clear the rabbit's bloodstream of certain colloidal materials, experiments were designed to indicate to what degree the blood clearance rate of a colloidal suspension of particles of a given size can be altered by the concurrent presence in the blood of a colloidal suspension of particles of different size. In these experiments the rate with which the reticuloendothelial system can remove a given, moderately large number of Au^{198} colloid particles from the circulation was compared to the rate with which the reticuloendothelial system can remove an identical number of Au^{198} particles if confronted simultaneously with a large number of circulating colloidal $CrPO_4$ particles. Conversely, the effect of Au colloid particles present in large numbers in the circulating blood on the clearance rate of Cr^{51} labelled $CrPO_4$ was delineated. The clearance rates were determined by continuously recording the concentration of radio-colloid in the blood by means of a side well scintillation crystal through which was channeled the blood flowing in an externally established carotid artery–jugular vein shunt. Repeated measurements of cardiac output by the dilution method, and repeated hepatic bloodflow measurements by quantification of the disappearance curves of low carrier Au^{198} colloid facilitated quantitative comparisons without neglecting the possibility of alterations in cardiac output and hepatic flow occurring during the acute experiments which may influence the hepatic "filtration" rate of radio-colloids.

R 7. *"Direct Assay of Co^{60} in Large Volumes of Urine."* ROGER L. VEATCH, CLARENCE F. DECKER, BRUNO KOTLOWSKI, and ERVIN KAPLAN (Radioisotope Research Section, Radioisotope Service, Veterans Administration Hospital, Hines, Illinois.)

A comparison has been made of the determination of Co^{60} in urine by radio-assay of precipitated Co^{60}, and by counting large volumes of the urine directly. The data obtained from urine of fifty patients undergoing the Schilling test indicates good agreement between the two

[1]Supported by Grant No. A-2848 from the National Institute of Health, USPHS.

methods, with the precipitation method yielding consistently lower values. In patients who showed a recovered level of activity below 10 percent, much better agreement between the two methods was found.

We suggest that the loss of activity indicated for the precipitation method may arise from incomplete Co^{60} precipitation. The advantages of performance speed and simplicity make the direct urine measurement using the Armac Auto-gamma spectrometer preferable to the precipitation method. In addition, it avoids the potential error of incomplete precipitation in the chemical method.

Technical Exhibits

Abbott Laboratories
North Chicago, Illinois

Atomium Corporation
Billerica, Massachusetts

Baird-Atomic, Inc.
Cambridge, Massachusetts

Curtis Nuclear Corporation
Gardena, California

Great Ideas Program
Toronto, Ontario

Harshaw Chemical Company
Cleveland, Ohio

Iso-Serve, Inc.
Cambridge, Massachusetts

Lanksverk Electrometer Company
Glendale, California

Nuclear-Chicago Corporation
Des Plaines, Illinois

Nuclear Consultants Corporation
St. Louis, Missouri

Packard Instrument Company, Inc.
LaGrange, Illinois

Picker X-Ray Corporation
White Plains, New York

Philips Electronic Instruments
Mount Vernon, New York

Radiation Counter Labs., Inc.
Skokie, Illinois

Scientific Products
Evanston, Illinois

Squibb, E. R. & Sons
New York, New York

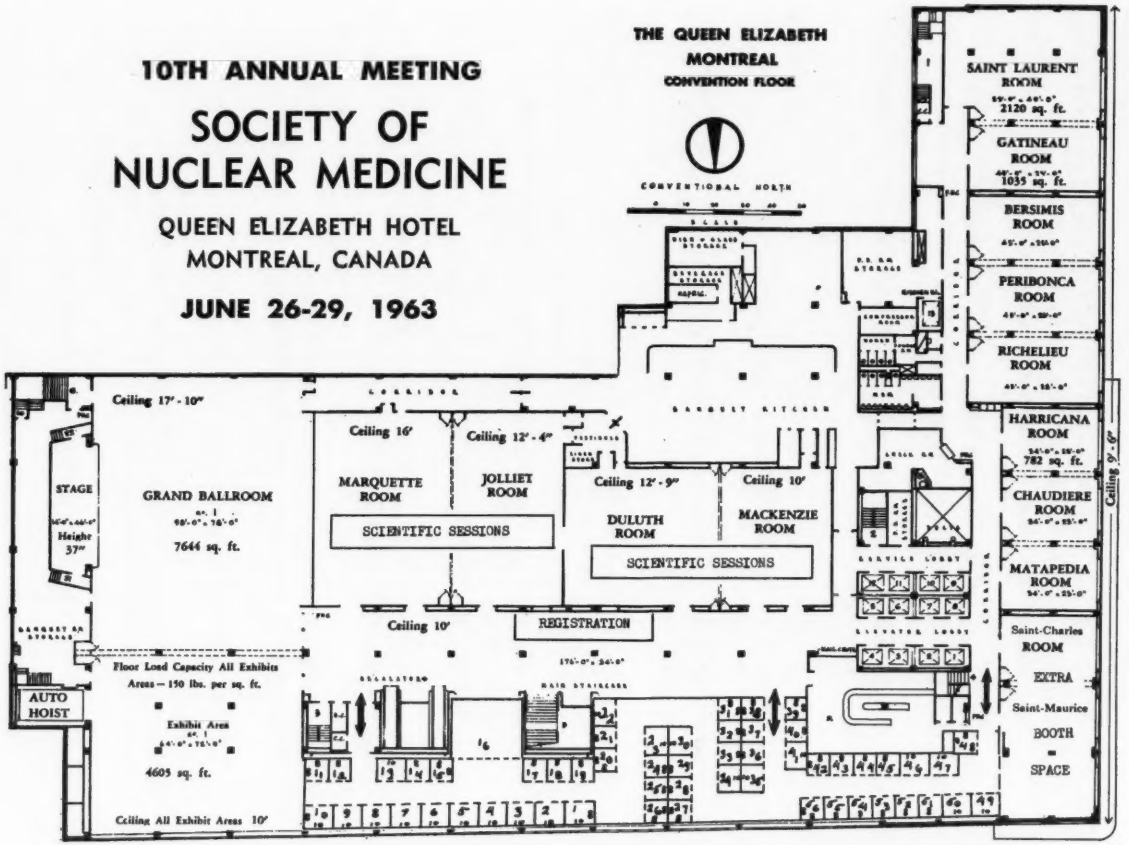
Volk Radiochemical Company
Skokie, Illinois

10TH ANNUAL MEETING

SOCIETY OF NUCLEAR MEDICINE

QUEEN ELIZABETH HOTEL
MONTREAL, CANADA

JUNE 26-29, 1963



Scientific Exhibits

Booth No.

Colloidal Radio Albumin Aggregates for Organ Scanning — S-42
G. V. Taplin, D. E. Johnson, E. K. Dore and H. S. Kaplan, Los Angeles, California and Torrance, California

Cancer Therapy by Intra-Lymphatic Injection of Isotopes — S-43
I. M. Ariel, M. Resnick, and D. Galey, New York

Principals of Rate and Its Applciation to the Renogram — S-44
S. Taplits, Cincinnati

Clinical Uses of the Scintillation Camera — S-45—S-46
H. O. Anger, Berkeley, California

Pancreatic Scanning with Selenium-75 Methionine — S-47
D. B. Sodee, Washington, D.C.

Digital Computer Analysis of Isotopic Data — S-49—S-50
J. H. Nodine and J. M. Platt, Philadelphia

The Role of Photo Scanning of Various Organs In a Small Community Hospital. — S-51
N. E. Herrera, Danbury, Connecticut

The Radioisotopic Renogram in Renovascular Hypertension — S-52
James L. Quinn III, and Joseph E. Whitley

Renograms and Cardiac Outputs with a Single Probe — S-53
D. Tabern and L. Holperin, Lake Bluff, Illinois

Contrast Enhancement of Photoscans by Photocopy Techniques — S-54
R. L. Libby, D. Ikkos, M. Gatsou, T. Doxiades, Los Angeles, California and Athens, Greece

Radiation Damage in Peripheral Blood Cultures from X-Rays and Radioisotopes — S-55
H. E. Duggan and D. L. Weijer, Edmonton, Alberta, Canada

Analog Computer Simulation of Radioiodine Tracer Studies in Thyroid Disease — S-56
A. L. Kretchmar and D. W. Brown, Oak Ridge, Tennessee

10th Annual Meeting

Thursday evening, June 27, 1963

SOCIAL HOUR AND ANNUAL BANQUET—GRAND SALON

6:45- 7:45 Social Hour—Cocktails (Courtesy of Technical Exhibitors)

8:00- 9:00 Annual Banquet (Dress Optional)

9:30-12:00 Dancing

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PRESIDENT'S ANNUAL REPORT

Dear Fellow Members:

As my year of service to you as President of your Society comes to a close, the biggest thing that I can see is that our world is changing faster than it has ever changed in all history. In the past two decades, we have gone through more change than people have experienced since the time of Christ.

Since we are in a new field, let us pause a moment to reflect on what has happened to our world. Today more than fifty-five per cent of the people industrially employed are working in jobs that did not exist fifty years ago. The armamentarium used in the practice of medicine today is comparatively new. Over ninety per cent of the drugs and medicines prescribed today had not been discovered thirty years ago. The greatest industrial employment in the United States today is in the Electronics, the Automobile, and the Aviation Industries. These were non-existent, or relatively unknown, fifty years ago.

I mention these points to emphasize that we must be geared to change. We must realize that we must keep abreast and make progress.

The past year has been eventful for our profession and we can look with a great deal of expectation into the future for the expansion of nuclear knowledge and its impact on nuclear medicine in all its applications. During the past year, you have been well represented by members of our Society at hearings in Washington on subjects of vital interest to our profession. This must continue.

With anticipated growth in the future, the duty continues to fall upon us to upgrade The Society of Nuclear Medicine on a national basis. The efforts by our Southeastern and Southwestern Societies of Nuclear Medicine in pioneering in this field by upgrading membership needs careful consideration. This can be done only by us as individuals acting on a Society basis by increasing our professional knowledge, by examinations, by education in our allied specialties, and by high ethical standards. I recommend for action establishment of a Fellowship Classification in the national level of membership and for an upgrading of membership requirements in general.

In addition, we have the important task of constantly blending the advances made in the nuclear medical field into the existing organizations dealing with medicine and the healing arts. This requires coordination and communication with the many organizations. The nuclear medical technician deserves our full support. The main task for this effort rests upon us to coordinate the training and registration for these technicians. Our plans must be made with this in mind, so that ultimately, the advances of nuclear medicine can be made available to every part of our Nation and beyond, by well trained nuclear technicians to assist in the nuclear medicine profession.

As you know through action of the Congress, the States have been taking over many of the responsibilities formerly exercised by the Atomic Energy Commission and this step alone should make it possible to extend the range of nuclear applications. However, in this process, we should do all that we can to assist those state agencies responsible and work with them as members of the various public boards and committees to assure that the interests of the members of the Society and the general public are being properly represented. This will be a continuing challenge which will be with us at least until the majority of the fifty States have accepted their responsibilities.

We must also give a good deal of attention to the workings of our government, particularly on the national level, so that we will know what is placed into law. It would seem to me that we must go beyond that and place ourselves in a position where The Society can have an important influence upon the shaping of legislation and plan so that we will not suffer from too much bureaucracy in our particular field. With the growth of control in Washington, this seems to be a most vital undertaking which must be dealt with more resourcefully and more effectively in the future. The effect of the legislation on drug uses and research (21CFR130 etc.) will be far reaching. We must keep informed and our opinions must be heard at top-level.

I believe that the suggestion of Craig Harris for representation by a competent individual with wide Washington acquaintance and high esteem be achieved. This can be done by obtaining the services of such a consultant for our Society, perhaps as a joint effort with other similar interest groups.

Since we know that the destructive power of nuclear energy is beyond the comprehension of man, so the constructive uses must be made to be beyond the present expectations. This task is clearly upon us as nuclear medical professionals in this new and exciting field. This is our world and our responsibility. This is an exciting time to be alive. Would that we could now see the ten years that will unfold before us to bring us to our Twentieth Anniversary. With the Lord's help, they will be even better than the ten just past.

J. R. MAXFIELD, M.D.
President

LADIES PROGRAM

10th Annual Meeting

LADIES' LOUNGE. The Richelieu Room on the Convention floor, will be open every day from 9:00 to 5:00; coffee will be served and members of the committee will be there to welcome you and assist you in any way possible. We hope this will draw people together informally and help make your visit a memorable one.

CHILDREN'S ACTIVITY ROOM. A room on the Convention floor (Peribonca Room) will be available for a variety of children's activities, depending upon the number and ages of the children.

Wednesday, June 26, 1963

1:00 P.M. Registration, Convention Foyer, Queen Elizabeth Hotel

7:30 P.M. Opening Session, University of Montreal

Thursday, June 27, 1963

9:00 A.M. Registration, Coffee, Richelieu Room

10:00 A.M. *City Tour:* This will include: Westmount Lookout, Chateau de Ramezay, Notre Dame Cathedral, Bonsecours—Sailors' Church, Luncheon at Helene de Champlain Restaurant on St. Helen's Island, provided through the courtesy of the CITY OF MONTREAL. Make-up demonstration by Lacome of Paris. Mansfield St. Entrance. Bus Charge—$2.00 per person

6:45 P.M. Banquet—Queen Elizabeth Hotel

Friday, June 28, 1963

9:00 A.M. Registration, Coffee, Richelieu Room

10:00 A.M. Montreal Museum of Fine Arts, Guided tour.
Start: Ladies' Lounge, Richelieu Room.
No Charge

Saturday, June 29, 1963

9:00 A.M. Registration, Coffee, Richelieu Room

10:00 A.M. Bersimis Room, Lecture, "What Do Our Husbands Do?"
Queen Elizabeth Hotel

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Professor Emilio Segrè[1]

Born in Tivoli (Rome) on February 1, 1905, son of Giuseppe Segrè, industrialist, and Amelia Segrè Treves. Went to school in Tivoli and Rome. Entered the University of Rome as a student of engineering in 1922. Transferred to the study of physics in 1927 and took his Doctor's degree in 1928 under Professor Fermi. His was the first Doctor's degree conferred under the sponsorship of Professor Fermi.

Served in the Italian Army in 1928 and 1929 and entered the University of Rome as assistant to Professor Corbino in 1929. In 1930 he had a Rockefeller Foundation Fellowship and worked with Professor Otto Stern at Hamburg, Germany, and Professor Pieter Zeeman at Amsterdam, Holland. In 1932 returned to Italy and was appointed Assistant Professor at the University of Rome, working continuously with Professor Fermi and others.

In 1938 Professor Segrè came to Berkeley, California, first as a research associate in the Radiation Laboratory and later as a lecturer in the Physics Department. From 1943 to 1946 he was a group leader in the Los Alamos Laboratory of the Manhattan District. In 1946 he returned to the University of California at Berkeley as a Professor of Physics, and still occupies that position. He was naturalized a United States citizen in 1944.

The work of Professor Segrè has been mainly in atomic physics and nuclear physics. In the first field he worked in atomic spectroscopy, making contributions to the spectroscopy of forbidden lines and the study of the Zeeman effect. Except for a short interlude on molecular beams, all his work until 1934 was in atomic spectroscopy. In 1934 he started the work in nuclear physics by collaborating with Professor Fermi on neutron research. He participated in the discovery of slow neutrons and in the pioneer neutron work carried on in Rome 1934-35. Later he intereseted in radio chemistry and discovered together with Professor Perrier the element technetium; together with Corson and Mackenzie the element astatine, and together with Kennedy, Seaborg, and Wahl, plutonium-239. In 1955 together with Chamberlain, Wiegand and Ypsilantis he discovered the antiproton. The study of antinucleons is now his major subject of research.

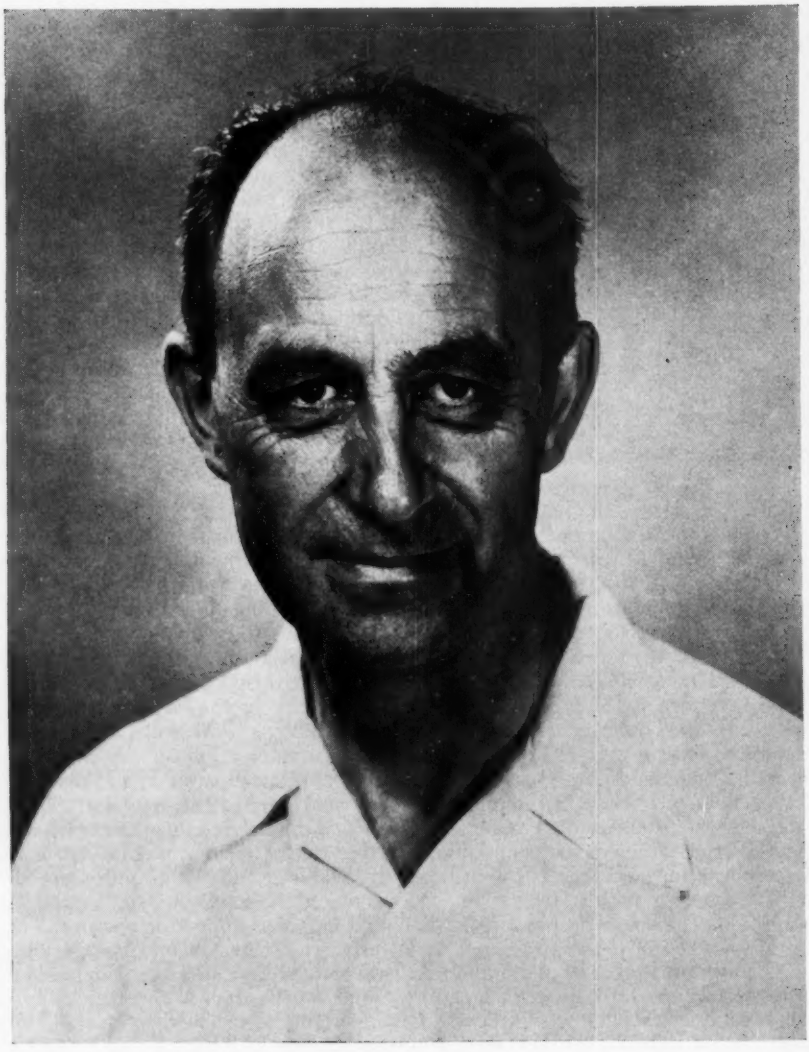
He has received the Hofmann Medal of the German Chemical Society and the Cannizzaro Medal of the Italian Accademia dei Lincei. He is an honorary Professor of San Marcos University in Peru and is a Dr. h.c. of the University of Palmero (Italy). Together with Owen Chamberlain, he received the Nobel Prize in physics, in 1959, for the discovery of the antiproton.

Professor Segrè is married to the former Elfriede Spiro and has three children.

---

[1]Professor Segrè will present the Fourth Annual Lecture—Nuclear Pioneer Series honoring Professor Fermi at the 10th Annual Meeting, Society of Nuclear Medicine, Montreal, Canada, June 28, 1963.

Honored by Fourth Annual Nuclear Pioneer Lecture 10th Annual Meeting Society of Nuclear Medicine.



ENRICO FERMI, 1901-1954. . .Noted Italian physicist and Nobel Prize winner who led the team of pioneer scientists that built the world's first nuclear reactor in an improvised laboratory in the racquets court under the West Stands of the University of Chicago's Stagg Field and on December 2, 1942, achieved the first self-sustaining nuclear chain reaction which gave mankind controlled release of the tremendous power of the atom.

Enrico Fermi, 1901-1954

Enrico Fermi, the brilliant Italian scientist who won the Nobel Prize for physics in 1938 and who headed the group of pioneer nuclear physicists that achieved the world's first controlled release of nuclear energy on Dec. 2, 1942, was born in Rome, Sept. 29, 1901.

Son of a railroad official, he studied at the University of Pisa from 1918 to 1922, and later at the Universities of Leyden and Göttingen. He became professor of theoretical physics at the University of Rome in 1927. Two years later, he was made a member of the Italian Academy.

Fermi became the leading figure of a group that revolutionized modern Italian physics and whose influence was felt in science throughout the world. His work at the University of Rome began the career that led him to equal fame as a theoretical and an experimental physicist.

Although preeminent in physics, Fermi also made major contributions to statistics of electron gas, the statistical model of the atom itself and fundamental contributions to the understanding of radioactivity.

In 1934, Fermi began to bombard atomic nuclei with neutrons, using small amounts of radon gas and beryllium as his source of neutrons. With simple equipment, elements beginning with the lightest (hydrogen) were bombarded and the chemical end products analyzed. Moving up the periodic table, Fermi and his associates came finally to uranium, then the heaviest known element. They found that the neutron bombardment had produced more than one element, and that at least one of the radioactive products seemed to be none of the existing elements close to uranium.

Their first report (May, 1934) did not claim discovery of a new element but described evidence they had found that such an element might be produced. Later analysis showed that the Fermi group actually had split the uranium atom but did not realize it at the time.

In a second series of experiments, it was discovered that by passing neutrons through other elements, they could be slowed down and the amount of artificial radioactivity produced could be increased greatly.

Fermi and members of his group obtained an Italian patent on this discovery. The patent rights were assigned to a friend in the United States, G. M. Giannini, who obtained an American patent in 1940. The status of this patent was not clarified until 1953 when the U. S. Atomic Energy Commission awarded $300,000 to the inventors.

These two series of experiments by Fermi were the essential precursors that led to the building of the world's first nuclear reactor. This work also brought him the Nobel Prize for physics in 1938.

In 1928, Fermi married Laura Capon, daughter of a highly respected and cultured Jewish family in Rome. He used the opportunity offered by the trip to Sweden to receive the Nobel Prize to get his family out of Italy, then under the Fascist regime of Mussolini. He brought his wife and two children—a daughter, Nella, and a son, Giulio—to the United States.

Fermi became a professor of physics at Columbia University. By this time, the phenomenon of nuclear fission was established and the tremendous release of energy involved has been calculated. Dr. George B. Pegram, dean of graduate studies at Columbia, designated Fermi to discuss the possible military potential of nuclear fission with Army and Navy officials in Washington in the spring of 1939.

Fermi was not successful in getting direct government backing for the work. But he was among those who persisted in the attempt to alert defense officials to

the possibilities of a nuclear bomb. The result was the historic Einstein letter to President Roosevelt in 1939 which began: "Some recent work . . . by E. Fermi and L. Szilard leads me to expect that the element uranium may be turned into a new and important source of energy . . ."

This letter led to the project that was to become the Manhattan Engineer District (MED) and produce the first nuclear weapon.

Working first at Columbia University and then at the MED operations at the University of Chicago, known as the "Metallurgical Laboratory," Fermi was placed in charge of building the world's first nuclear reactor. Success came on Dec. 2, 1942, in a dark racquets court under the West Stands of the University's Stagg Field, when the first self-sustaining nuclear chain reaction was achieved with this reactor.

Later, Fermi was transferred to the weapon design laboratory at Los Alamos, New Mexico, as chief of the advanced physics department. When the war ended, the University of Chicago established the Institute for Nuclear Studies. Fermi joined its staff along with some other scientists who had worked at the "Met.Lab."

For his work on the nuclear bomb, Fermi was awarded the Medal of Merit in 1945. The Presidential citation read, in part:

"First man in all the world to achieve nuclear chain reaction and as associate director of the Los Alamos Laboratory, Manhattan Engineer District, Army Services Forces, his essential experimental work and consulting service involved great responsibility and scientific distinction. . ."

Although Stagg Field stadium has been torn down, the plaque placed there on the fifth anniversary in 1947 remains at the site. It reads:

"On December 2, 1942, man achieved here the first self-sustaining chain reaction and thereby initiated the controlled release of nuclear energy."

On the 10th anniversary, 1952, Fermi spoke again at a gathering of many of the men who had been in the racquets court on the historic occasion.

At the Institute, the great physicist continued his investigations, concentrating on the particles that make up the nucleus. He was interested particularly in the short-lived particles—the mesons—which make up part of the "glue" that holds the nucleus together.

He was a consultant in the design of the synchrocyclotron at the University of Chicago and used this particle accelerator (atom smasher) in his studies. In the last year of his life, 1954, Fermi made an important contribution to nuclear physics by a correct interpretation of a phenomenon involving the behavior of polarized beams of protons.

Fermi became ill with cancer and died in his Chicago home on Nov. 28, 1954.

Posthumously in 1954, he was the first recipient of what is known now as the Fermi Award, presented annually by the President of the United States. This first award, signed by President Eisenhower, said: "An Award of Merit to Enrico Fermi for his contributions to basic neutron physics and the achievement of the controlled nuclear chain reaction."

He was awarded numerous honorary degrees by universities in the United States and abroad and was a member of many scientific societies, including the National Academy of Sciences and the Royal Society of England. Fermi was a member of the General Advisory Committee to the U. S. Atomic Energy Commission from its organization late in 1946 until August, 1950.

Fermi was a good "team worker" and more than 100 of the 240 publications that bear his name were produced in collaboration with his colleagues. Among the nine books he wrote, one—done early in his career in Italy—was a text on physics for high schools. His works are being collected and published by the University of Chicago Press.

JOURNAL OF NUCLEAR MEDICINE 4:231-233, 1963

PRELIMINARY PROGRESS NOTE†

Selenomethionine Reappearance in Blood Following Intravenous Injection[1,2]

William H. Oldendorf, M.D. and Masami Kitano, M.D.

Los Angeles

INTRODUCTION

During the course of studies of brain permeability to several compounds labeled with gamma-emitting radioisotopes we had occasion to study selenium[75] labeled methionine.[3] As a part of the technique we follow the antecubital venous blood levels of the labeled compound starting at two minutes after its intravenous injection. Most substances show a roughly exponential fall-off in the circulating blood. However, with selenomethionine we encountered a rapidly falling blood level with a minimum level reached at about 30 to 45 minutes as noted in Figure 1. The blood level of selenium then rose to approximately three-quarters of the two minute level. It remained stable at this level and then slowly fell, reaching 30 per cent in about 7 days. It is the purpose of this preliminary report to note this early disappearance and reappearance of selenomethionine.

Technique: Five healthy males aged 32 to 42 received by antecubital injection 10 microcuries of selenium[75] labeled methionine (Squibb). After a 2 minute period required to obtain reasonably complete blood pool mixing, antecubital samples were drawn periodically from the arm opposite the injection. The injections were made in the morning 1 to 2 hours after breakfast.

The blood specimens were anticoagulated with small amounts of sodium citrate and 4 cc's of the blood was pipetted into test tubes which were then counted in a commercial well counter.

To test the hypothesis that the selenium noted in the blood after the blood level had resumed its final stable value was protein bound, an attempt at crude localization in a protein fraction was obtained by precipitating the globulin with sodium sulfate and precipitating the plasma protein with trichloracetic acid and checking the supernatant isotope content. It was determined in the 4 hour blood specimen that all of the selenium precipitated with trichloracetic acid.

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[1]From the Neurology Section, Wadsworth General Hospital, Los Angeles Veterans Administration Center and the Division of Neurology, University of California at Los Angeles.

[2]This work was in part supported by United States Public Health Service grant number NB-02575-03.

[3]Donated by Squibb Radiopharmaceuticals.

†Preliminary Progress Note announcement on page 243.

After precipitation of globulin with sodium sulfate approximately 25 per cent of the radioactivity remained in the supernatant and 75 per cent was precipitated. Upon further precipitation of protein from this supernatant with trichloracetic acid a negligible radioactivity representing less than 2 per cent of the original activity remained in the supernatant.

From this preliminary attempt at crude isolation these data suggest that approximately three-fourths of the selenium was in the globulin fraction of the blood protein.

DISCUSSION

Selenium[75] labeled methionine was introduced by Blau and Manske. (1) Their technique of biosynthesis has been described. (2) These authors introduced this compound in an attempt to visualize the localization within pancreas of parenterally injected methionine.(1,2) Their work suggests that a significant proportion of labeled methionine is picked up by pancreas but presumably the majority is picked up by the liver.

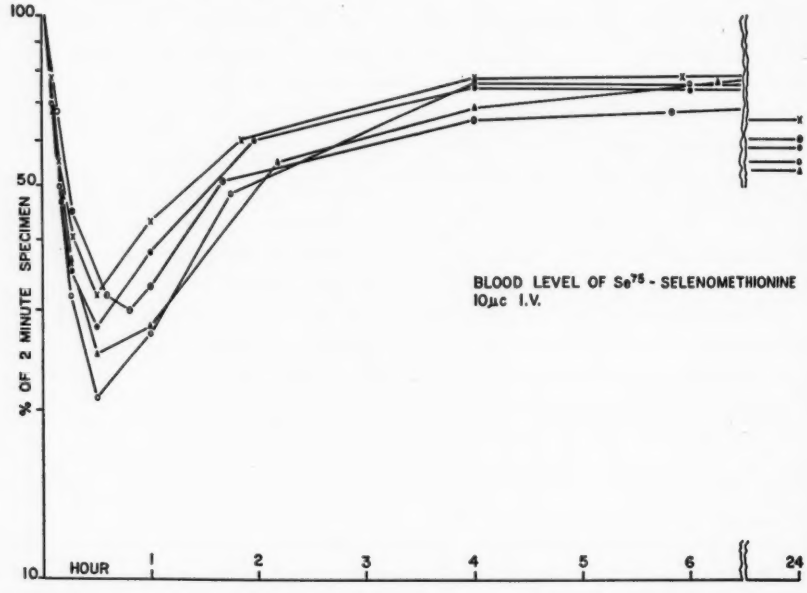

Fig. 1. Showing the blood levels of selenium[75] after its intravenous injection as selenomethionine at 0 minutes. Blood specimens were commenced at 2 minutes to allow adequate mixing. It is important that all values are shown relative to this 2 minute value. Since the blood level is falling precipitously at this time slight inaccuracy due to the time of sampling results. This must be considered when the final stable value is measured. If, for example, the initial blood specimen actually were inadvertently drawn at 3 minutes one would expect to find the final plateau level would be higher when plotted relative to this early value, as we have done here. For this reason the variation in the level to which the selenium[75] has returned in the blood probably largely is accounted for by unavoidable variations in the time of drawing the initial specimen.

Methionine metabolism using sulfur^{35} labeling has been studied by Friedberg, Tarver and Greenberg. (3,4) and Kinsell *et al* (5). However, none of these studies include any detailed measurement of blood S^{35} levels during the first hour. The precise biologic equality between selenomethionine and methionine containing sulfur is not completely established. However, insofar as our technique with selenomethionine and earlier studies with an S^{35} label are comparable, they behave similarly.

We have speculated in explaining the reappearance in the circulating blood of the injected selenomethionine that it is rapidly picked up by the liver, incorporated into blood proteins and returned to the blood. However, it should be evident that more precise localization with accurate fractionation techniques is required before the chemical localization of this material in the blood is adequately established.

Since the work reported here is entirely on drawn blood specimens it is not necessary to use a gamma-emitter and the same study could be carried out with sulfur^{35} labeled methionine. It would be of considerable interest if sulfur^{35} methionine showed a similar disappearance and reappearance.

SUMMARY

1. Following its intravenous injection selenomethionine disappears rapidly from the blood, reaching a minimum concentration at 30 to 45 minutes. The selenium level in the blood then rises, becoming constant at a level about 75 per cent of the blood level found at 2 minutes following injection. 2. After the blood level has been re-established the selenium seems to be protein bound and our preliminary crude analysis suggests that it is predominantly in the globulin fraction of the blood protein. 3. The chemical form of the selenium^{75} noted in the blood should be studied in more detail with more precise fractionation techniques.

ACKNOWLEDGEMENT

The authors wish to acknowledge the technical assistance of C. Duncan Everett, B.S.

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JOURNAL OF NUCLEAR MEDICINE 4:234-238, 1963

The Prevention of Hepatic Metastasis By the Use of A Colloidal Suspension of Radioactive Chromic Phosphate ($CrP^{32}O_4$)[1]

Arthur S. McFee, M.D., Norman B. Ackerman, M.D., and Merle K. Loken, Ph.D., M.D.

Minneapolis

INTRODUCTION

The problem of the hepatic metastasis has been one of the most frequent stumbling blocks in the treatment of visceral cancer. Frequently, its presence alone is reason enough for considering a patient doomed. Many techniques of dealing with the problem of the established metastasis have been proposed: excision, radiation, local organ perfusion, (1) or direct injection of the nodes of tumor with radioactive isotopes. (2) Cole has effectively demonstrated the presence of tumor emboli in venous drainage from the G.I. tract at surgery, (3) and has proposed treatment of these emboli with chemotherapeutic agents (4) at the time of and subsequent to surgical intervention. A series of articles by Fisher has probed many of the factors influencing the "take" of liver metastasis, such as injury to the liver, (5) the number of cells in a metastatic bolus (6) in the portal vein, and numerous other factors. The treatment of an established metastasis is, by and large, unsuccessful. Attention has recently been more and more focused on the prevention of metastases. Fisher has shown that repeated laparotomy and mechanical manipulation of the liver may well activate tumor cells present in the liver which would otherwise remain dormant. (5) Cole's work has indicated that beyond 48 hours after tumor injection, attempts at prophylaxis of metastases with chemotherapeutic agents were generally unsuccessful. (4)

Colloidal suspensions of isotopic substances are removed largely into the reticulo-endothelial system of an organism. (2, 7, 8) It would seem logical then that a dose of colloidal chromic phosphate administered in the portal vein of an animal would provide a significantly high level of intense radioactivity which would be retained locally in the liver. This might act to prevent the "take" of metastatic cells from a bolus of tumor cells administered also via the portal vein. The purpose of this study is to investigate the effectiveness

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of colloidal chromic phosphate in the prevention of hepatic metastases from an administered tumor bolus.

METHOD

Female albino Holtzman rats weighing 150-200 grams were used in this study. A Novikoff hepatoma was employed as the insulting tumor. This strain of tumor has been kept in our laboratories for some months. Initial empirical tests showed us that a dose of 100,000 cells of this tumor in the portal vein could be expected to produce excellent metastatic tumor within 2 weeks in 70 per cent of the rats so treated. (Fig. 1). The tumor injection was prepared by homogenizing solid tumor obtained from intraperitoneal implants in a Potter-Elvehejm tissue homogenizer. The homogenates were prepared with normal saline and diluted with approximately 25 vols of saline for each volume of tumor. The diluted suspension was then assayed directly in the red cell portion of a standard hemocytometer. Appropriate aliquots were taken to provide a constant dose of 100,000 cells per injection. In separate syringes, doses of colloidal chromic phosphate suspension amounting to 75 microcuries per dose were prepared.

Each animal received an injection of tumor cells. This was followed by an injection of colloidal chromic phosphate at varying times. One group of animals was pretreated with chromic phosphate 24 hours prior to receiving tumor. Celiotomy was performed on every animal and all the injections were made directly into the portal vein. At the end of 2 weeks, the animals were explored. In some instances, the animals were saved and reexplored at a later date. All results as to the presence or absence of tumor are related to the

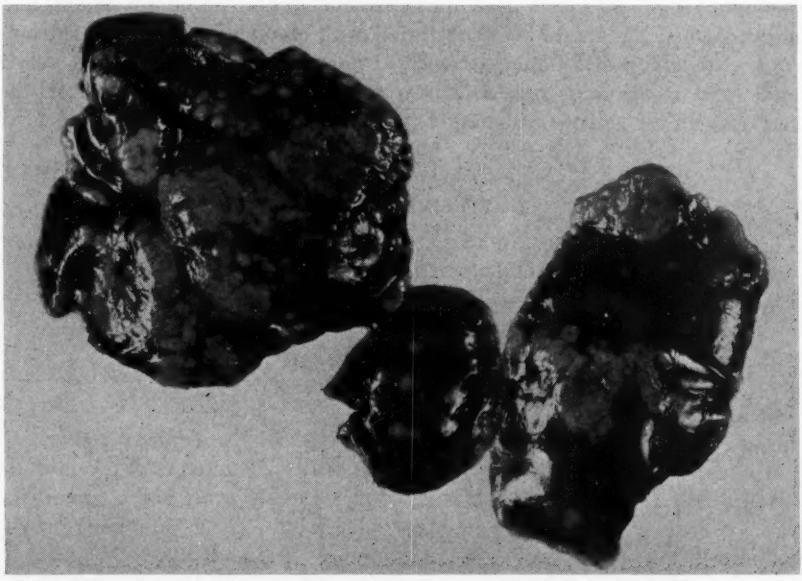

Fig. 1. Metastatic Tumor in the liver of a rat 2 weeks after injection of 100,000 cells.

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findings at two weeks. Later findings were taken as confirmatory only, because exploration and manipulation alone has been found to increase the "take" of metastases nearly fourfold. (5)

A total of 138 animals has been studied. (Table I) These fall into 5 groups:

1. Controls receiving only tumor injections— 44
2. One minute animals receiving tumor injections followed by chromic phosphate 1 minute later— 26
3. Sixty minute animals receiving tumor injections followed by chromic phosphate 60 minutes later— 26
4. Twenty-four hour animals receiving tumor injections followed by chromic phosphate 24 hours later— 26
5. Twenty-four hour pretreated animals receiving chromic phosphate twenty-four hours before the tumor— 16

These injections were carried out in runs of twelve to sixteen animals, with participants in each group being included in each run. Control animals were randomly interspersed in each run some receiving tumor injections toward the end of the run and some at the beginning. Tumor cells in this type of homogenate retain their viability for a matter of 2-3 hours. With interspersed controls, we felt we had some control of this problem of aging of cells.

RESULTS

In these animals, a rate of tumor take in the controls of 75 per cent was noted. This fell to 31 per cent in the one-minute group, 38 per cent in the 60 minute group and 42 per cent in the 24-hour group. Essentially no effect was observed when the animal was pretreated with chromic phosphate. (Table II)

A sixth group of 24 animals received only chromic phosphate. At varying times, up to sixteen days, these animals were sacrificed in groups of four and their livers assayed for activity per minute per gram of tissue. An initial drop in de-

TABLE I

EXPERIMENTAL PLAN

PREVENTION OF HEPATIC METASTATIC DISEASE EXPERIMENTAL PLAN
ALL INJECTIONS INTRAPORTAL

Group	*Number of Animals*	*Tumor*	*$CrP^{32}O_4$*
Control	44	100,000 cell	None
1 Minute	26	100,000 cell	75 μc 1 min. $\bar{p}$ tumor
60 Minutes	26	100,000 cell	75 μc 60 min. $\bar{p}$ tumor
24 Hours	26	100,000 cell	75 μc 24 hrs. $\bar{p}$ tumor
24 a	16	100,000 cell	75 μc 24 hrs. before tumor.
P^{32} Control	6	None	75 μc
P^{32} Time Study	24	None	75 μc

TABLE II

RESULTS IN TERMS OF PERCENT "TAKES" OF METASTATIC TUMOR

PREVENTION OF HEPATIC METASTATIC DISEASE RESULTS

Group	*Number of Animals*	*+ For Tumor*	*− For Tumor*	*% "Take"*
Control	44	33	11	75%
1 Minute	26	8	18	31%
60 Minutes	26	10	16	38%
24 hour	26	11	15	42%
24 Hour a	16	12	4	75%

tectable radio-activity of 25-30 per cent by the third day was noted, after which the levels of radiation, corrected for physical decay, maintained a fairly high constant average. (Fig. 2) These findings are taken as confirmatory that the major portion of the administered radioactivity stays in the liver. Using the in-

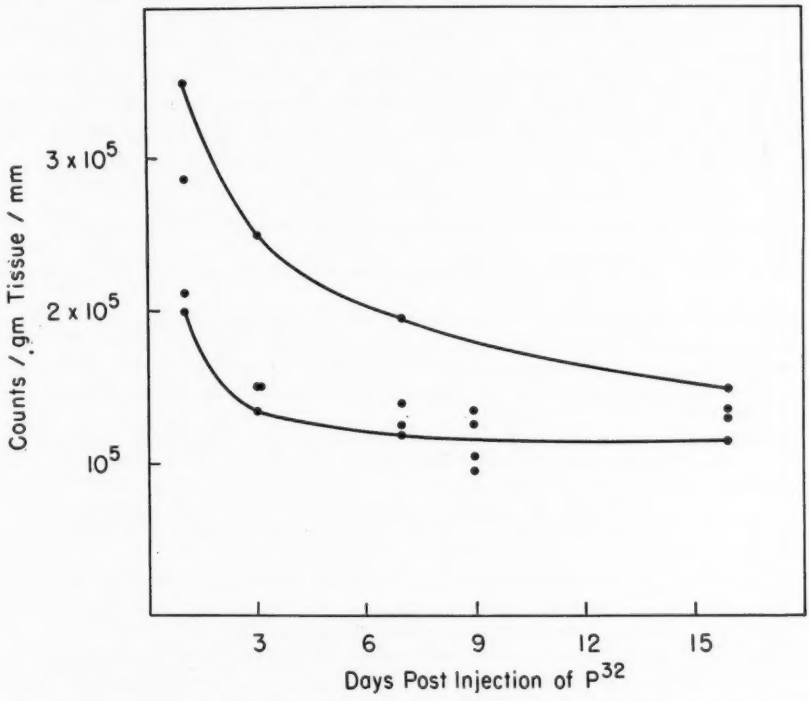

Fig. 2. Specific activity in counts/gm tissue/min., corrected for physical decay of chromic phosphate, in liver, plotted as a function of time.

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formation shown in Figure 2 for the localization of P^{32} in the rat, together with a knowledge of the characteristics of the decay of this isotope, one may readily calculate the average dose delivered to the rat liver. (9) This is found to be 2725 rad.

A seventh and final group of six animals received chromic phosphate only in August 1961. After one year, these animals were sacrificed and their livers were examined histologically. In all instances the hepatic structure was normal. Occasional collections of macrophages and inflammatory cells were seen, consistent with the history of having injected an unsterile particulate suspension. Very infrequent platelet thrombi were also observed. There was no evidence of cirrhosis or scarring.

DISCUSSION

This study is aimed at a method for the prevention of hepatic metastasis, not for its treatment. The method itself could be easily made an adjunct of any intra-abdominal procedure. The doses of P^{32} employed here are in the low therapeutic range. On a gram for gram basis, Ariel (2) used more than twice this dose for treatment of metastatic nodules interstitially. The doses we have used are apparently well tolerated. Speculatively, we might expect some more successful results with an increased dose.

SUMMARY

A method for the prevention of hepatic metastatic disease via the portal vein by use of intraportal colloidal chromic phosphate has been presented. Reduction in the number of metastases over control animals by 50 per cent has been observed.

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JOURNAL OF NUCLEAR MEDICINE 4:239-243, 1963

Comparative Thyroid-Function Studies with the Resin T-3 Test[1]

Francis H. Foeckler, Jr., Sc.D., Nellie May Bering, M.T. (ASCP), Joanne Siragusa, M.T. (ASCP), and Oscar B. Hunter, Jr., M.D.

Washington, D.C.

In 1955 Hamolsky (1) introduced a thyroid-function test based on the uptake of I^{131} labeled l-triiodothyronine (T-3) by erythrocytes *in vitro*. By mixing red cells from one donor with plasma from another, he showed that the plasma was the decisive factor governing the per cent uptake by the red cells. Plasma from hyperthyroid, euthyroid and hypothyroid persons yielded uptakes consistent with their status, and this was independent of the thyroid status of the red cell donor. In both this investigation and others in 1957 (2) and 1959 (3), the author and co-workers found that the red cell uptake of T-3 yielded results as diagnostically accurate as those of standard methods. The same conclusion was reached by Sterling (4), Koons (5), Ureles and Murray (6), Robbins (7) and Crigler *et al.* (8) in 1959, and by Fries (9) and Christensen (10) in 1960.

Mitchell (11) reported in 1958 on the binding of thyroxin by synthetic resin, and in 1961 and 1962 Scholer (12, 13) described a resin technique which measures directly the amount of I^{131} labeled T-3 taken up by plasma. The author reported good clinical results in over 500 tests.

Circulating thyroxine appears to be bound mainly to a protein fraction between the alpha 1 and alpha 2 serum globulin, measured by electrophoresis at pH 8.6. To a minor extent it appears to be bound to albumin and to an area corresponding to the pre-albumin range when assessed electrophoretically. If the globulin binding sites are highly staturated with the patients own hormone, as in hyperthyroidism, then but little T-3 will be bound by the plasma *in vitro*, and the red cells will bind the remaining large amount of unbound T-3. Conversely, if the protein binding sites are transporting a small amount of the patients own hormone, as in hypothyroidism, a large amount of T-3 will be bound by the plasma *in vitro*, and the red cells will bind the remaining small amount of free T-3.

The purpose of this investigation was to compare the results of Scholer's resin technique with those of the Hamolsky red-cell method in the hope of replacing the latter, more cumbersome test with the former, which is rapid and simple to perform.

[1]The Oscar B. Hunter Memorial Laboratory, Washington 6, D.C.

MATERIALS AND METHODS

The labeled resin was prepared as follows according to Scholer (12, 13). To a 25 ml flask were added 15 ml distilled H_2O, 2.5 micrograms of I^{131} labeled l-triiodothyronine[2] and 5 grams (dry weight) of anion exchange resin[3]. The mixture was shaken at 37° C for 30 minutes, the resin was then filtered, washed over with distilled water and allowed to dry at room temperature. 0.1 gram portions of this resin were added to glass test tubes (150 x 15 mm). The tubes were counted in a standard well counter and the amount of resin in each tube was adjusted to give approximately equal (within 2%) activity. They were kept at room temperature until use.

Standard plasma was prepared by pooling the plasmas from 20 euthyroid persons. The plasmas to be tested and the standard plasma were treated identically as follows:

1. 2 ml plasma were added to each resin tube.
2. The stoppered tubes were shaken at 35° C for 90 minutes, and the resin was allowed to settle to the bottom of the tube.
3. 1 ml of plasma was removed from each tube, and its activity was measured in the well counter.
4. Calculations: (The pooled standard plasma was given a thyrobinding index of 1).

$$\text{The thyrobinding index of the test plasma} = \frac{\text{activity in test plasma}}{\text{activity in standard plasma}}$$

Results:

Hyperthyroid:	less than .86
Euthyroid:	.86 to 1.20
Hypothyroid:	greater than 1.20

RESULTS

Our first attempts with the Scholer resin technique resulted in failure. The large amount of radioactivity of the labeled resin caused the well counter to jam, with the result that the radioactivity of the individual tubes could not be standardized, a prerequisite for performing the test. In preparing a stock of labeled resin, Scholer's method calls for 2.5 mcg T-3 per 5 g resin (dry weight), the individual test being performed with 0.1 g resin in 2 cc plasma. The amount of T-3 per test is 0.05 mcg. With the Hamolsky method, however, only 0.001 to 0.012 mcg T-3 is used per test with 3 cc whole blood. We therefore labeled 5 g resin (dry weight) with 0.25 mcg T-3, giving 0.005 mcg of the hormone per test. This amount is roughly in the middle of the range of concentration recommended by Hamolsky. With this modification we were able to perform successfully the Scholer resin test.

Before adopting the resin technique as standard procedure in our laboratory,

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[1]Triomet, Abbott Oak Ridge, Tenn.

[2]Amberlite IRA-400, Analytical, Rohm and Haas Co., Phila., Pa.

we tested the blood of 100 subjects by both the Hamolsky and Scholer (our modification) methods and compared the results. Of the persons tested, 70 were clinically euthyroid, 25 hyperthyroid and 5 hypothyroid. In all cases of hyperthyroidism and hypothyroidism, and in 10 euthyroid subjects, the thyroid uptake of inorganic I^{131} was also measured. In general, we found excellent correlation of the Thyrobinding Index with the per cent uptake of T-3 by the red cells, and the *in vitro* findings were confirmed by the *in vivo* uptake of I^{131} in those cases where the latter test was also performed.

However, in patients who had received either therapeutic or diagnostic doses of inorganic I^{131} before drawing blood for the T-3 tests, the results of the two methods were often contradictory. It was the Hamolsky red cell method which always agreed with the clinical picture. A somewhat better correlation was obtained when the PBI^{131} of the test plasma was determined before performing the resin test. The activity due to the PBI^{131} was then subtracted from the total activity in the test plasma, thereby indicating the actual amount of T-3 I^{131} bound by the plasma:

$$\text{TBI} = \frac{\text{Total activity in plasma—activity due to } PBI^{131}}{\text{activity in standard plasma}}$$

In such cases we found that if 80 per cent or more of the I^{131} was protein bound, then the results usually correlated with those of the red cell uptake. However, when more than 20 per cent of the I^{131} was inorganic (*i.e.* not protein bound), the results of the two methods were usually contradictory. The rate of exchange of inorganic I^{131} between plasma and resin was not known in these cases, and further experimentation may throw more light on this problem.

After completing these preliminary studies, we adopted the Scholer labeled-resin technique, with our modification, as the routine T-3 test in our laboratory. However, the Hamolsky method has been kept both as a standard reference source and as the regular procedure in cases where patients have received inorganic I^{131} before blood has been drawn for the T-3 test.

Table I summarizes the findings in 1,100 T-3 determinations using our modification of the Scholer labeled-resin technique.

TABLE I

THYROBINDING INDEX OF PLASMA USING OUR MODIFICATION OF THE SCHOLER LABELED-RESIN TECHNIQUE

Clinical Status	*Number of Cases*	*TBI Range*	*% Outside of Range*
Euthyroid	975	.86 to 1.20	4% below .86 8% above 1.20
Hyperthyroid	100	< .86	3%
Hypothyroid	25	> 1.20	10%

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CONCLUSION

We found our modification of Scholer's I^{131}-labeled-resin technique to be an accurate test of thyroid function in most cases. Its chief advantage over the Hamolsky method is its rapidity and ease of performance, important factors to the clinical laboratory with a heavy daily load of T-3 determinations. However, the resin technique cannot at present replace completely the Hamolsky red cell method, because the results of the former, at least with our modification, are not always accurate in cases where the patient has received diagnostic or therapeutic doses of I^{131}.

SUMMARY

1. We were able to perform successfully the Scholer Thyrobinding Index test by labeling anion exchange resin (IRA 400) with approximately 0.005 micrograms I^{131}-l-triiodothyronine, instead of with 0.05 micrograms as proposed by Scholer.

2. The bloods of 100 subjects were tested by both the Hamolsky and Scholer (our modification) methods, and we found good correlation between the two tests and the clinical picture.

3. These *in vitro* findings were confirmed by the *in vivo* uptake of I^{131} in 5 cases of hypothyroidism, 25 cases of hyperthyroidism, and in 10 euthyroid subjects.

4. Tracer or therapeutic doses of I^{131} can invalidate the results of the resin technique.

5. In an additional 1,100 cases, we found good correlation between our modification of the Scholer resin technique and the clinical picture of thyroidism.

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Announcement to Authors

Preliminary Notes

Space will be reserved in each issue of THE JOURNAL OF NUCLEAR MEDICINE for the publication of one preliminary note concerning new original work that is an important contribution in Nuclear Medicine.

Selection of the preliminary note shall be on a competitive basis for each issue. One will be selected after careful screening and review by the Editors. Those not selected will be returned immediately to the authors without criticism. Authors may resubmit a rejected or revised preliminary note for consideration for publication in a later issue. The subject material of all rejected manuscripts will be considered confidential.

The text of the manuscript should not exceed 1200 words. Either two illustrations, two tables, or one illustration and one table will be permitted. An additional 400 words of text may be substituted if no tables or illustrations are required. Only the minimum number of references should be cited.

Manuscripts should be mailed to the Editor, Dr. George E. Thoma, St. Louis University Hospital, 1325 South Grand Blvd., St. Louis 4, Missouri. They must be received before the first day of the month preceding the publication month of the next issue, e.g., preliminary notes to be considered for the September, 1963 issue must be in the hands of the Editor before July 1, 1963.

JOURNAL OF NUCLEAR MEDICINE 4:244-248, 1963

The Use of a Modified Radioactive Test for Evaluating the Peripheral Circulation.[1]

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INTRODUCTION

Non-radioactive techniques used for evaluation of peripheral circulation such as calorimetry, oscillometry and plethysmography are all indirect, and liable to marked technical errors and variations due to physiologic and environmental factors that are not easy to control and interpret. In contradistinction, methods utilizing radioactive isotopes have the advantage of being a direct way to obtain data representing the peripheral blood flow.

Blumgart & Yens (1) were the first workers to use radioactive substances in this field. Later, better techniques were introduced when artificial radioactive isotopes became available and more sensitive equipment was manufactured. In order to avoid the difficulties that were encountered in earlier radioactive methods as diffusibility and irregular distribution; Krieger *et al* (2) suggested the use of radioactive iodinated human serum albumin for evaluating the peripheral circulation. The validity of this test was proved by the same workers.

The aim of the present study is to present some modifications in the procedure and calculations of this test; to make it easier to perform; less time consuming; and more informative.

MATERIALS & METHODS

This report includes 42 subjects of different age groups, ranging from 18 to 65 years. All were in-patients at Cairo University Hospitals. They were examined for evidence of atherosclerosis in the form of palpable radial arteries, absent peripheral pulse, arteriosclerotic heart disease, arteriosclerotic encephalopathy, retinal atherosclerosis, and arteriosclerotic gangrene.

The test was performed in a quiet room, free from draughts and with a relatively constant temperature. Twenty microcuries of the radioactive iodinated human serum albumin (RISA) in 1 ml of saline were injected into the antecubital vein. The radioactivity uptake curve was measured by a scintillation de-

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tector placed in contact with the ball of the foot. The scintillation detector was attached to a counting rate meter with a time constant of 3 seconds, and a strip chart recorder moving at a rate of 2 cm per minute. When the uptake curve reached a plateau, 10 mg. tolazoline hydrochloride (Priscol®) were injected intravenously. Three minutes later, another equal dose of RISA was administered and the same procedure repeated.

CALCULATIONS

The difference between the uptake curves obtained before and after the application of Priscol® is calculated as percentage of the original uptake curve. This is well illustrated in Figure 1 by $B/_A$ X 100. These areas are either measured by a planimeter, or calculated according to the following equation:

$$\text{Area} = N_F\,(t - 0.69\,T_{\frac{1}{2}})$$

Where N_F is level of activity at 10 minutes

t is time and equals 10 minutes

$T_{\frac{1}{2}}$ is time to reach 50 per cent of plateau activity

This equation has been arrived at by integrating the equation:

$$N = N_F\,(1 - e^{-\lambda t})$$

RESULTS

The percentage increase in the radioactivity uptake curve after Priscol® in the 30 normal subjects included in the present study was 56 per cent ± 17 (Mean ± 1 S.D.), with a range from 30 to 91 per cent. In one of the cases this value amounted to 158 per cent. Being the only case in which the level was so high and far from the range that has been previously stated, it was decided to exclude this case from calculations of the mean. Figure 2 illustrates the mean of the results obtained in the normal subjects.

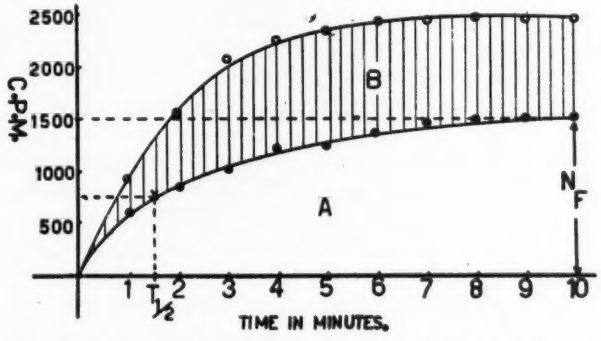

Fig. 1. Radioactivity build-up curve of a normal person to demonstrate the method of calculations.

Area = $(N_F\,(t - 0.69\,T_{1/2})$

A original uptake curve

B increase in uptake curve after Priscol®

Final result = $\frac{B \text{ X } 100}{A}$

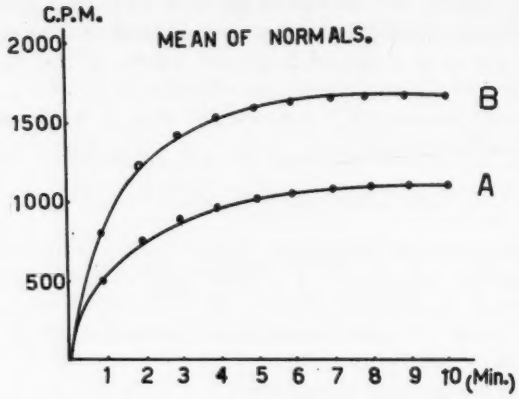

Fig. 2. Mean radioactivity build-up curve of the normals before (A) and after (B) Priscol®.

In the 12 patients who had clinical evidence of atherosclerosis the average increase in the radioactivity uptake curve after the administration of Priscol® was 15 per cent ± 7 (Mean ± I S.D.), having a range of 2 to 25 per cent. The mean of the results of patients with restricted peripheral circulation is shown in Figure 3.

As regards time taken by radioactivity to reach plateau, there was not much difference between normal and abnormal subjects; the range being 3 to 9 minutes. After the injection of Priscol® this time interval dropped by one to three minutes in all the normal cases; while in subjects with abnormal peripheral circulation this effect was not constant and was lesser in degree.

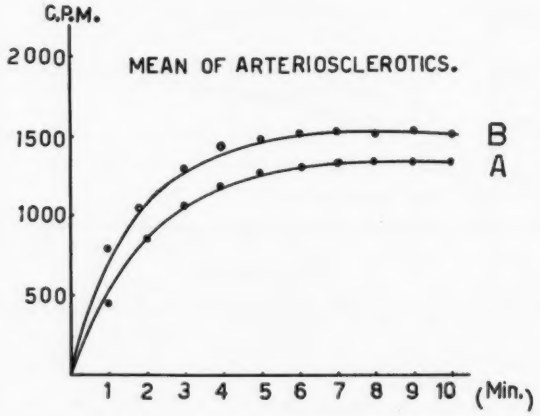

Fig. 3. Mean radioactivity build-up curve of patients with restricted peripheral circulation before (A) and after (B) Priscol®.

DISCUSSION

The use of radioactive isotopes for evaluation of peripheral circulation was introduced in 1927 by Blumgart and Yens (1) using radium C. Realizing the drawbacks of this test, investigations continued to find better techniques. These began to appear after 1944 due to the production of artificial radioactive isotopes and the manufacture of more sensitive equipment. But, these methods still suffered from several disadvantages as irregular distribution which was noticed when using tagged red cells (3), and the physicochemical and osmotic phenomena associated with diffusion of electrolytes if radioactive sodium (4, 5) or phosphorus (6) was used.

To obviate these difficulties, the use of radioiodinated human serum albumin to test the peripheral circulation was introduced and validated by Krieger et al (2) in 1952. With the aid of two detectors placed in close contact with both feet, they compared radioactivity build-up in the two limbs following the intravenous injection of 75 microcuries of RISA. In order to evaluate the ability of the vessels to dilate; the whole process was repeated after the application of heat through an electric device put around the limb for 30 minutes, and the results compared with the previous ones. According to this group of workers the slope of that segment of radioactivity build-up curve from time of arrival till plateau indicated the rate of mixing of radioactive albumin with normal palsma in the capillary bed surveyed by the detector. This rate of mixing depended on blood flow through the capillary bed. Moreover, the height of the plateau represented the size of the vascular bed seen by the detector used.

In the present study, 20 microcuries of RISA were injected in each step. This amount is much lower than previously used; making the procedure safer for the patient. In addition Priscol® which is known to be a more effective dilator for vessels of lower limbs than warning (7) was used; thus decreasing the time needed for this step from 30 to 3 minutes. Furthermore, the new method of calculation has the advantage of covering the earlier segment of the radioactivity build-up curve as well as the plateau measured before and after dilatation. Thus, the blood flow through the capillaries, the size of the vascular bed seen by the detector and the ability of the vessels to dilate are all taken into consideration in the final result.

The results obtained in the present study agree with the clinical evidences and show good separation between normals and those with restricted circulation. In normal subjects the result was above 30 per cent, while in patients with abnormal peripheral circulation it amounted to 25 per cent or less.

SUMMARY

The best available radioactive method for evaluation of the peripheral circulation is that discussed by Krieger *et al* (2) using radio iodinated human serum albumin. In the present work some modifications have been introduced in this technique. These modifications are:

(1) Lowering the dose of RISA
(2) The use of Priscol® instead of heat to dilate the vessels.

(3) The increase in radioactivity build-up curve is calculated as the percentage of the original uptake curve. This amounted to 56 per cent ± 17 in normals, with a range from 30 to 91 per cent. In those with restricted peripheral circulation it was 15 per cent ± 7, ranging between 2 and 25 per cent. These results agreed well with the clinical evidences in all the cases examined.

ACKNOWLEDGMENT.

I wish to record my thanks to Dr. W. J. MacIntyre for his invaluable help and advices.

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JOURNAL OF NUCLEAR MEDICINE 4:249-258, 1963

The Association of Thyroid Cancer and Prior Irradiation in Infancy and Childhood[1]

Raymond G. Rose, M.D., James E. Hartfield, M.D., Mavis P. Kelsey, M.D., and Eleanor J. Macdonald, A.B.

Houston, Texas

Shortly after 1900, the introduction of ionizing radiation gave man both a tool and a hazard. The damaging effects of x- and gamma rays on human tissue were recognized from the beginning. The interest in the dangers of radioactivity from medical, industrial, experimental, and natural sources has been heightened by increased awareness of related carcinogenic effects. The list of radiation-related tumors is a long and growing one. In animals, tumors of the bone, ovary, and thyroid (1, 2, 3), as well as leukemia (4), can be induced by irradiation. Of special interest is the observation that the production of thyroid tumors in rodents by irradiation or radioactive iodine (I^{131}) is enhanced by the administration of antithyroid drugs. This finding suggests that radiation may be the initiating factor, and goitrogens or thyroid-stimulating hormones (5) the promoting factor (6). In man, irradiation induces tumors of the skin (7), sarcomas of the bone (x-rays and radium) (8, 9), carcinoma of the liver (thorotrast) (10), lung (uranium) (11), pharynx and larynx (x-rays) (12, 13), plus leukemia (atomic bomb fall-out, radiologist's occupational exposure, x-ray treated patients with ankylosing spondylitis, and patients with thyroid cancer treated by radioactive iodine) (14 to 16) (Table I).

The association of prior irradiation with the development of cancer of the thyroid first discussed in 1949 by Quimby and Werner (17), and first noted in infancy and childhood in 1950 by Duffy and Fitzgerald (18) following irradiation to the thymus has since been reported in differing proportions by many scien-

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[1]From the Endocrine-Isotope Service, Department of Medicine, and the Department of Epidemiology, The University of Texas M. D. Anderson Hospital and Tumor Institute and The University of Texas Postgraduate School of Medicine, Houston, Texas.

tists. (Table II). The ideal definitive study, wherein study subjects are exposed in infancy and controls are not and both are followed through maturity, is not possible in ethical medical practice. Consequently, attempts are made to find the best possible controls and to qualify resultant reports or to describe cases in a cancer population, with or without a history of radiation exposure, obtaining the history of exposure retroactively.

In the latter group of studies, among children with thyroid cancer, a high incidence of prior irradiation to the head, neck, and upper chest area during childhood, is reported in fourteen papers (19 to 32). Winship and Rosvoll's series (32) shows such a history in 229 of 286 children with thyroid cancer, with an average latent period of 8.6 years between irradiation and the development of the cancer. It is probable that many of these instances of thyroid cancer among children are the same cases that appear in other reports, as Winship and Rosvoll's series includes cases from many institutions.

DISCUSSION

Since the first patient was admitted in March, 1944, through August, 1961, 426 patients of all ages with thyroid cancer have been seen at The University of Texas M. D. Anderson Hospital and Tumor Institute. These 426 cases have been reviewed for this study. Attempts have been made since 1959 to contact all living patients. Of the 350 living at the beginning of this review, a total of 216 had replied by 1962. The other 76 had died prior to 1962. In 1960, when replies had been received from 175 patients, punch-carded abstracts of these 175 patients' histories were sent to the Strang Cancer Prevention Clinic of the Memorial

TABLE I

LATENT INTERVAL IN TUMORS INDUCED BY RADIATION

Site	*Number of Cases*	*Range (years)*	*Mean (years)*
Skin (43)	94	4–14	9.0
Skin (44)	220	4–17	7.8
Skin (45)	—	4–21	14.0
Skin (7)	21	4–42	27.5
Bone (46)	24	3–11	6.0
Bone (47)	11	5–22	11.2
Bone (9)	38	3–22	8.6
Leukemia (14, 15, 16)	25	<1–13	6.2
Pharynx (12)	32	10–35	25.5
Larynx (12)	6	8–22	14.0
Thyroid (32)	229	—	8.6

Sloan-Kettering Cancer Center in New York City. They were matched for ethnic group, *i.e.*, Latin American, negro, and others, for exact age and year of admission, and, insofar as possible, for residence or general geographical area, with the presumably well Strang patients. The detailed physical examinations made of patients at Strang, and the accompanying thorough case histories are comparable to those made on patients at M. D. Anderson Hospital. Through the cooperation of Dr. Emerson Day, head of the Strang Cancer Prevention Clinic of the Memorial Sloan-Kettering Cancer Center in New York City, and Miss Eleanor M. Hassett, his statistician, this comparison was possible. The analysis in this report will be based on the total of 216 who replied, except for the portion which describes the findings among the 175 patients matched with the Strang experience.

In the total series replying, 70 gave a positive history of previous irradiation. Reports were verified by subsequent contact with the physicians who administered the irradiation.

In Table III, the age distribution at time of diagnosis of the 216 patients with thyroid cancer and history of prior irradiation is shown. Both the children under 10 years old had a positive history of irradiation. Since irradiation of the thymus in infants, and of acne in adolescents and adults was introduced in the 1920's and 1930's, individuals who were adult by that time would rarely have had irradiation for those conditions. As would be expected, the proportion with a positive history of irradiation did decrease progressively with the advance in age. Thirteen of the 17 children (76.0 per cent) under the age of 15 had a positive history of irradiation. Four patients who were 15 years old at diagnosis had a positive history. Of 33 patients under the age of 20, 20 had received prior irradiation therapy (60.0 per cent).

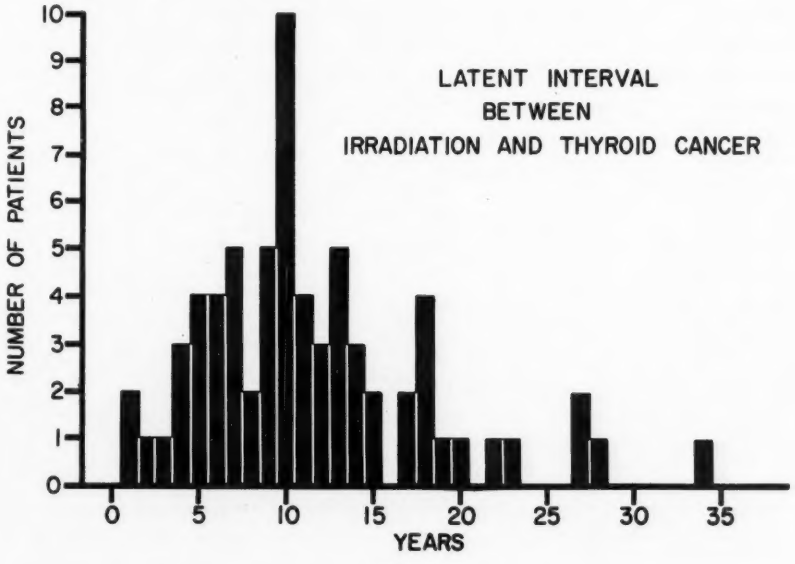

Fig. 1

As will be observed in Table IV, the most common indication for which irradiation (25 patients) had been given previously was acne, with exposure to the element including the combined face, neck, and upper chest areas. Irradiation for enlarged thymus accounted for only five cases. The exact dosage of irradiation was learned in 16 instances and ranged from 225 r to 6,300 r (Table V). The physicians reporting did not routinely include in their replies the exact dosages administered. In this series of 70 patients, the latent period between irradiation and diagnosis of thyroid cancer averaged 12 years (Fig. 1).

Simpson, Hempelmann, and Fuller (33) did a retrospective study on irradiated children using their nonirradiated siblings as controls to see if thyroid cancer was more often present in children with prior irradiation than in their nonirradiated brothers and sisters. They found that the incidence of thyroid cancer which developed in the irradiated children was much higher than would be expected. They calculated an expected instance of 0.06 cases and found 8 in the 2,394 irradiated children and found none in the 2,400 sibling controls (33 to 35).

Confirmatory findings were later reported by Simpson (33, 34), Saenger (36),

TABLE II

THYROID CANCER IN CHILDREN UNDER FIFTEEN YEARS OF AGE

	Total	*Irradiation History*	*Per cent*
Quimby (17)	10	3	33.3
Duffy[xb] (18)	28	10	36.0
Clark (19)	15	15	100.0
Majarakis (21)	10	10	100.0
Fetterman (23)	10	8	80.0
Hayles (24)	41	30	73.0
Howard (26)	3	3	100.0
Wilson (27)	7	7	100.0
Buckwalter[b] (28)	8	3	38.0
Petit* (29)	11	9	82.0
Uhlmann*[a] (41)	25	4	16.0
Rooney (30)	10	7	70.0
Raventos (31)	22	11	50.0
Warren[b] (20)	23	1	4.0
Asper[x] (22)	18	13	72.0
Crile (25)	14	11	78.0
Winship (32)	286	229	80.0
Present Series	17	13	76.0

x = under 18 years
b = thymic irradiation only
* = under 21 years
a = tonsil irradiation only

Quimby (37), Latourette (38), and Maloney (48), and contradictory findings by Garland (39), Conti (40), Uhlmann (41), and Snegireff (42) (Table VI.) In Conti's report (40), patients received treatment to the thymus through small 4 × 4 cm ports and in smaller dose (150 r) than the apparent threshold level of 200 r observed by Simpson. Other studies with relatively negative results were based on series that were either too small or in which too short a period of time had elapsed to allow for a substantial positive or negative result.

The comparison of the 175 Anderson thyroid cancer cases matched with the Strang cases was made, with full realization that qualifications would be necessary, as an attempt to find the best kind of controls available. The patients at M. D. Anderson Hospital were the same age at the same time as were the controls, and were examined the same month and year. Many of the thyroid patients at M. D. Anderson Hospital are in the same economic group as the Strang patients. The thoroughness of history taking and of physical examinations is comparable. The Strang draws on a population from all over the country. Region of residence was approximated with the M. D. Anderson cases as far as was possible.

In Table VII, the comparison of occurrence of prior irradiation of M. D. Anderson thyroid cancer patients with Strang controls shows a significantly higher history of irradiation in cancer patients than in those with no previous irradiation. The table separates the group with irradiation to the head, neck, and

TABLE III

HISTORY OF PRIOR IRRADIATION IN CHILDHOOD IN M. D. ANDERSON HOSPITAL SERIES 1944–1961

Age Group	*Total Series*	*Total with Known History*	*Positive History of Prior Irradiation*	*Per cent of Total with Prior History*
0–9	2	2	2	100.0
10–19	31	31	18	58.0
20–29	65	47	20	43.0
30–39	91	53	18	34.0
40–49	77	32	7	22.0
50–59	67	25	2	8.0
60–69	57	17	1	6.0
70–79	31	8	2	25.0
80–89	4	1	0	0
Not Stated	1	0	0	0
Total	426	216	70	32.0

TABLE IV

AREAS RECEIVING PRIOR X-RAY THERAPY IN M. D. ANDERSON HOSPITAL SERIES

Area	*Number*
Head and Neck	
Acne	25
Tonsils	8
Dermatitis	4
Cervical Adenitis	3
Adenoids	2
Thyrotoxicosis	2
Miscellaneous	5
Subtotal	49
Chest	
Thymus	5
Bronchitis	4
Postmastectomy	2
Dermatitis	1
Breast	2
Subtotal	14
Miscellaneous	
General Exposure	
In Utero	1
Generalized Eczema	1
Abdomen	
Carcinoma, Cervix	1
Uterine, "Fibroids"	1
Arms, Hands (Eczema)	1
Mid Back (Tuberculous Spondylitis)	1
Bursitis	1
Subtotal	7
TOTAL	70

TABLE V

DOSAGE OF PREVIOUS X-RAY THERAPY TO HEAD, NECK, AND CHEST AREAS IN M. D. ANDERSON HOSPITAL SERIES

Dosage	*Number of Cases*
200–400 r	3
400–600 r	1
600–800 r	4
900–1,200 r	5
1,500 r	1
Greater than 1,500 r	2
Total	16

chest to emphasize the greater occurrence of cancer in individuals with prior irradiation to this area. This confirms the experimental evidence found in the laboratory of a cause and effect mechanism between irradiation of the thyroid gland area of animals and the increased likelihood of developing thyroid cancer. It has been suggested by Doniach (6) that irradiation is the initiating factor, and that the stimulation of the thyroid gland during its growth and develop-

TABLE VI

FOLLOW-UP ON IRRADIATED CHILDREN

	Number Irradiated	*Thyroid Cancer*	*Controls*[z]	*Thyroid Cancer*
Simpson (33, 34)	2,394	8	>2,400	0
Saenger (36)	1,644	11	3,777	0
Quimby (37)	144	8		
Latourette (38)	867	1		
Garland (39)	1,780[y]			
Conti (40)	1,564*	0		
Uhlmann (41)	480[x]	0		
Snegireff (42)	148	0		
Maloney (48)	125	2		

y = "many but not all cases traced"
* = 1,300 patients received 150 r or less, 4 x 4 cm. ports
x = 2,500 patients treated but only 480 traced
z = expected incidence 0.06 cases of thyroid cancer per 1,000

ment in infancy and childhood is the promoting factor in the subsequent development of thyroid cancer.

CONCLUSIONS

1. Review of the literature has revealed a growing volume of reports associating irradiation of the thymus or of the head and neck area, during infancy and adolescence, with subsequent development of cancer of the thyroid.

2. Of the 426 individuals with thyroid cancer seen at The University of Texas M. D. Anderson Hospital and Tumor Institute from 1944 through 1961, 216 replied to questionnaires concerning prior irradiation. Of this number, 70 reported a positive history of preirradiation. Acne was the most common reason given for therapy. The latent interval between irradiation and onset of cancer averaged 12 years.

3. Both of the children under 10, thirteen of the 17 patients under 15, and twenty of the 33 patients under 20 years of age at time of diagnosis of thyroid cancer had a history of previous irradiation.

4. The evidence gathered to date is provocative enough to suggest caution in the use of irradiation in the management of benign conditions of the head, neck, and chest in infants and children.

TABLE VII

COMPARISON OF OCCURRENCE OF PRIOR IRRADIATION OF M. D. ANDERSON HOSPITAL PATIENTS (CANCER OF THE THYROID) AND STRANG MATCHED CONTROL PATIENTS (NO CANCER)

	Previous Irradiation	*No Previous Irradiation*	*Total*
M. D. Anderson	46	129	175
Strang	10	165	175
Total	56	294	350

	Previous Irradiation to Head, Neck, and Chest	*No Previous Irradiation to Head, Neck, and Chest*	*Total*
M. D. Anderson	40	135	175
Strang	2	173	175
Total	42	308	350

Significantly higher history of irradiation was found in cancer patients.
Probability of above results being caused by chance alone was less than 1 in 1,000. $p < .001$

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Determination of Coronary Blood Flow Index by External Scintillation Detection[1,2]

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INTRODUCTION

The measurement of human coronary blood flow has long been a challenge in clinical medicine. The only currently accepted technique is the nitrous oxide method, (1) which has the disadvantage of requiring a cardiac catheterization for coronary sinus sampling. Furthermore, it does not permit frequent repetition. Efforts to adapt radioisotope dilution curves to the determination of coronary flow date back to the work of Waser and Hunzinger, (2) who attempted to measure coronary transit time utilizing external detection of P^{32}. Pritchard, MacIntyre, and Moir (3) were unable to confirm their results.

Efforts to detect the coronary inflow by precordial monitoring of the passage of a radioactive bolus through the heart and coronary arteries have been made by Sevelius and Johnson (8). Their method depends upon defining a "third peak" in the precordial curve following the right ventricular and the left ventricular peaks. This third peak is regarded as the coronary arterial filling phase and it is quantitated by extrapolating the second or left ventricular washout slope and the third peak washout slope. The area enclosed by the two extrapolations is used to calculate coronary blood flow. This "coronary" peak which is said to occur in the middle of the downslope of the left ventricular washout appears to us to be theoretically unsound and we are unable to find it in curves which we have obtained from precordial radiation monitoring.

A new concept has been introduced by the observation that the dilution curve of a radioactive bolus has a slower disappearance rate when monitored over the

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[2]Supported in part by Rockefeller Foundation Grant #RF—61139, and grant in aid from Kellogg Foundation.

heart than when sampled from a peripheral artery. It was postulated that this difference was due to coronary blood flow. Similar studies on patients with known coronary heart disease showed no such difference in disappearance rates.

This observation led to an investigation in animals (5) designed to define the mechanism of production of the heart curve distortion and to a clinical study designed to test whether or not quantitative or qualitative estimation of human coronary blood flow might be obtained by simultaneous monitoring of a dilution curve from two sites on the body, the precordium and an arterial reference site.

Animal experiments and theoretical considerations were presented in a previous paper (5). This paper reports the findings which have lead to the use of the occipital region of the brain as a reference point for external monitoring of the arterial dilution curve. Also reported are data obtained by comparing simultaneous brain and precordial isotope dilution curves in normal subjects and ischemic heart disease patients. The effects on these measurements of reserpin in normal and ischemic heart disease patients are also reported. Physical characteristics of the instrumentation and technique are described.

CLINICAL MATERIAL AND METHODS

Fifty-nine non-coronary subjects included surgical patients without evidence of heart disease. 33 were normal males and 26 were normal females. 38 patients with myocardial infarcts were referred from the in-patient and out-patient population of the Department of Cardiology—Catholic University Hospital. The age and sex distribution of all subjects are included in Table I. All were studied by the following technique:

The non-fasting subject lies supine on an examining table with his head projecting from the end of the table and the occiput resting on the aperture of the shielding of a scintillation detector. This detector is oriented 15° backward in the saggital plane, so that it points away from the thorax and neck. Two ½ inch thick lead shields are interposed between the detector and the thorax. This shielding and orientation of the probe are essential in order to minimize backscatter from the thorax and to avoid inclusion of neck muscles in the scope of the probe.

TABLE I

AGE, SEX AND CFI DISTRIBUTION OF PATIENTS STUDIED BY EXTERNAL DETECTION.

	NORMAL MALES		NORMAL FEMALES		INFARCTS	
Age	*Number*	*C F I*	*Number*	*C F I*	*Number*	*C F I*
21–30 years	9	1.34	3	1.34		
31–40 years	9	1.34	17	1.59	8	1.13
41–50 years	11	1.32	3	1.51	7	1.16
51–60 years	2	1.48	2	1.65	17	1.16
61–70 years	2	1.64	1	1.68	8	1.07
TOTAL	33		26		38	

The precordial detector is placed over the apex of the heart and flat against the chest wall. It usually covers the area from the third to fifth intercostal spaces between the mid-clavicular and anterior axillary lines (Fig. 1).

Both scintillation detectors have NaI crystals of 2″ × 1″ diameter recessed 4

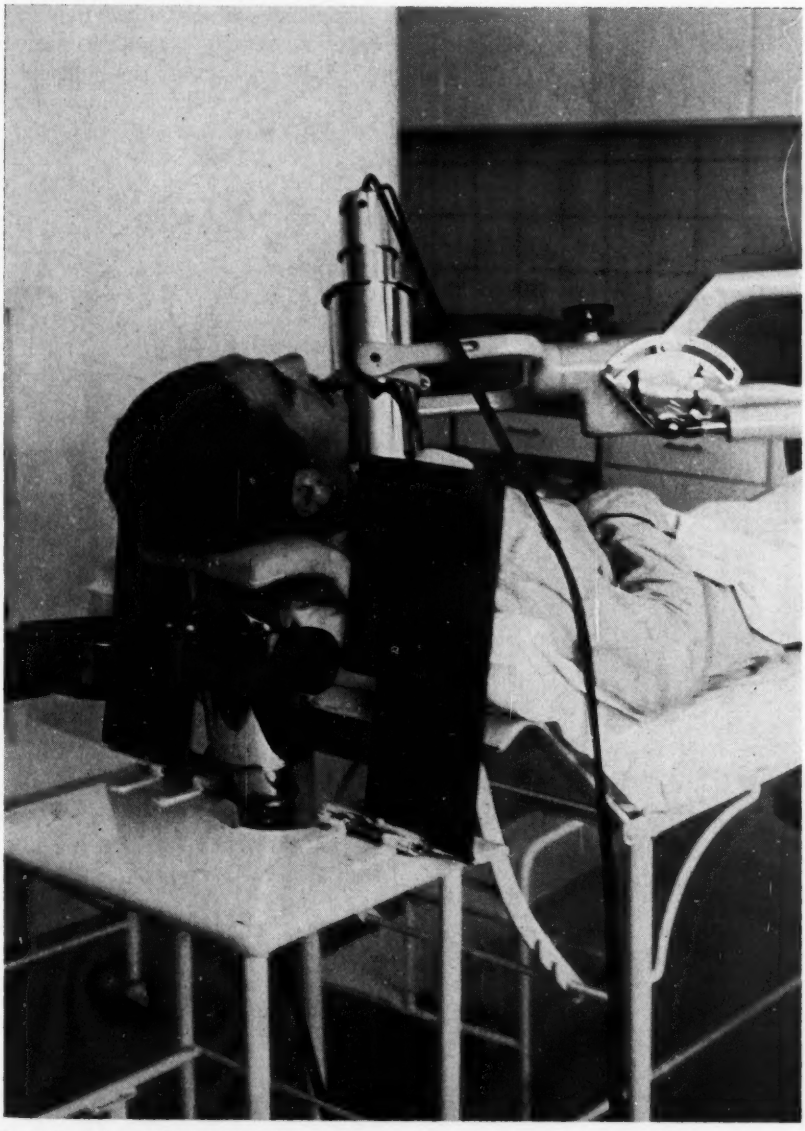

Fig. 1. Position of scintillation detectors during determination of coronary flow index.

cm with a 2″ diameter collimation. Both detectors are connected to a dual events per unit time (EPUT) meter which is set to record total counts during each 1.3 seconds. The total counts for successive 1.3 second periods are printed on an adding machine tape, without display time.

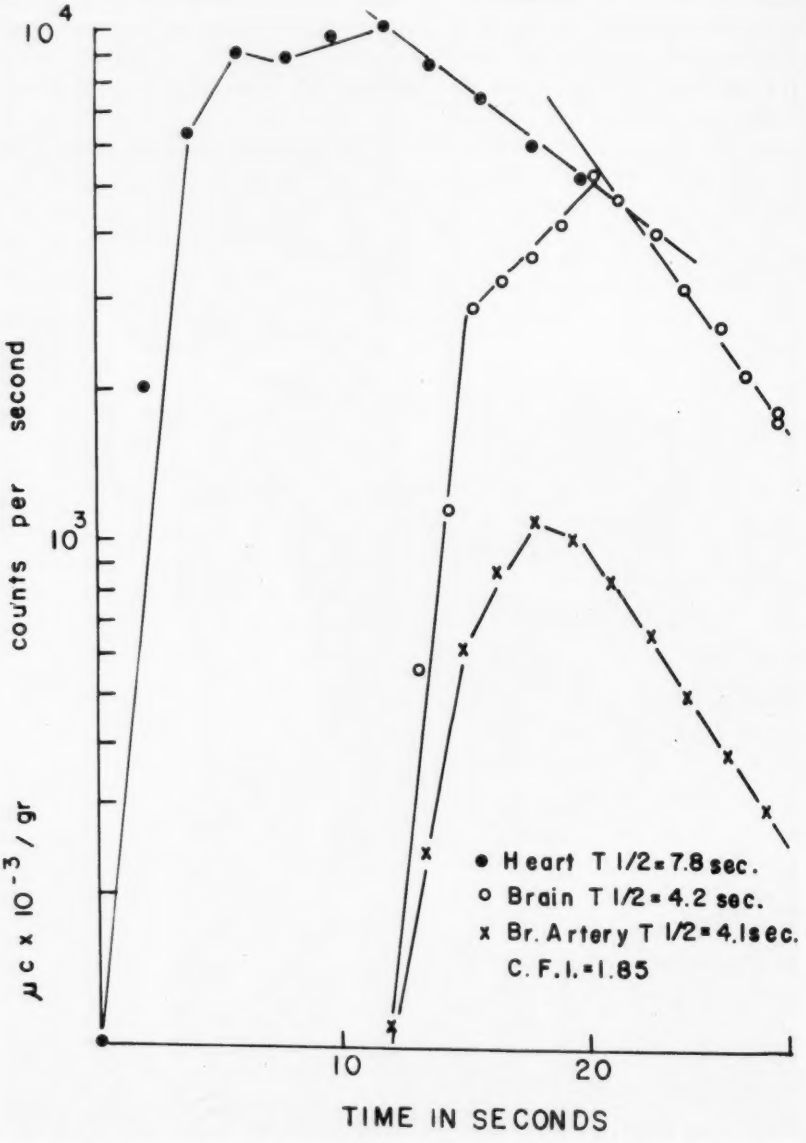

Fig. 2. Normal subject. External scintillation detection of heart and brain curves and simultaneous direct sampling from brachial artery.

Discrimination levels are set to discriminate against radiation below 150 kev energies.

The technique of injection is important to insure a good bolus effect. The largest antecubital vein is chosen and the arm elevated and adapted until semi-collapse of the vein walls is observed. In this position a dose of 80 microcuries of radio iodinated serum albumin (RISA) I^{-131} in a volume of one cc is quickly injected through a number 21 needle. Recording is begun at the moment of injection and concluded when a well defined recirculation plateau is reached in the brain channel.

The EPUT meter furnishes information in terms of absolute counts per unit

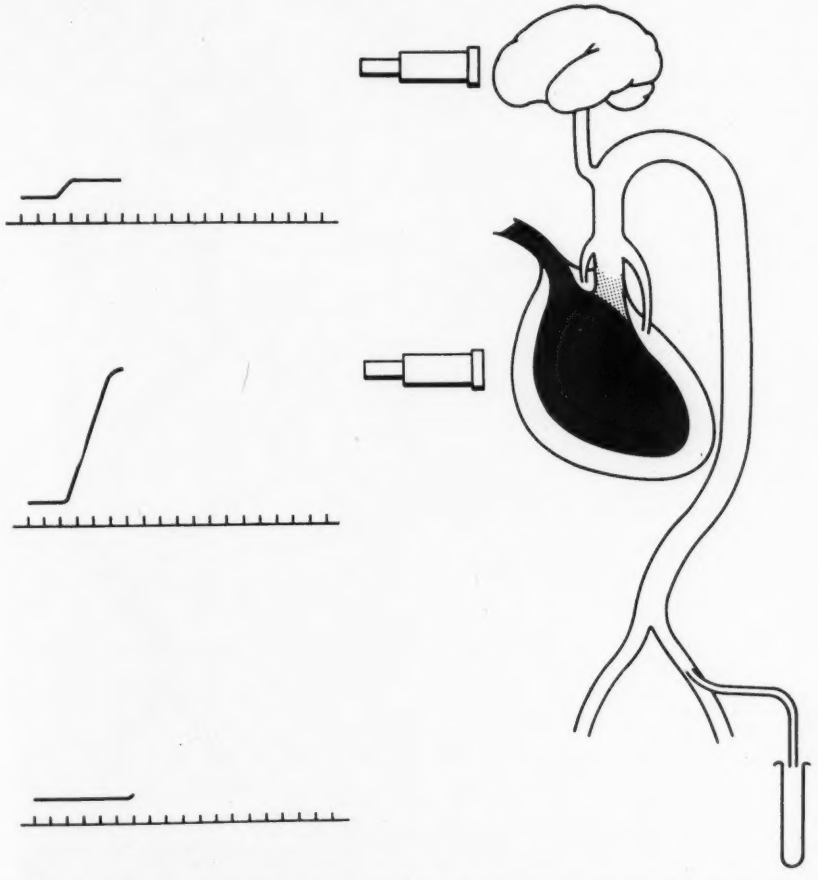

Fig. 3A. Schematic representation of recording of: (A) passage of radioactive bolus through heart chambers, (B) appearance in arteries and brain, (C) emptying of heart chambers and filling of coronary vascular bed brain and femoral artery, and (D) arrival of recirculation.

time. The recorded data are plotted against time on semi-log paper. A double peaked curve is observed from the precordial probe as the radioactive bolus traverses the right and then the left heart cavities. If the positioning of the heart probe is correct; *i.e.*, closer to the left ventricle than to the right ventricle, then the left heart peak is the highest one. This left heart peak is followed by an exponential drop of counts to slightly below the 50 per cent level, where it levels off to a plateau. The maximum counting level observed is in the range of 8,000 to 10,000 counts per sampling period. The background of the heart probe is 30 counts per 1.3 seconds, giving a ratio of peak to background of at least 300 for a first determination. The heart downslope is determined as a straight line on semi-log paper. The time required to drop to the 50 per cent of any given valve is measured on this line ($T\frac{1}{2}$ heart) (Fig. 2).

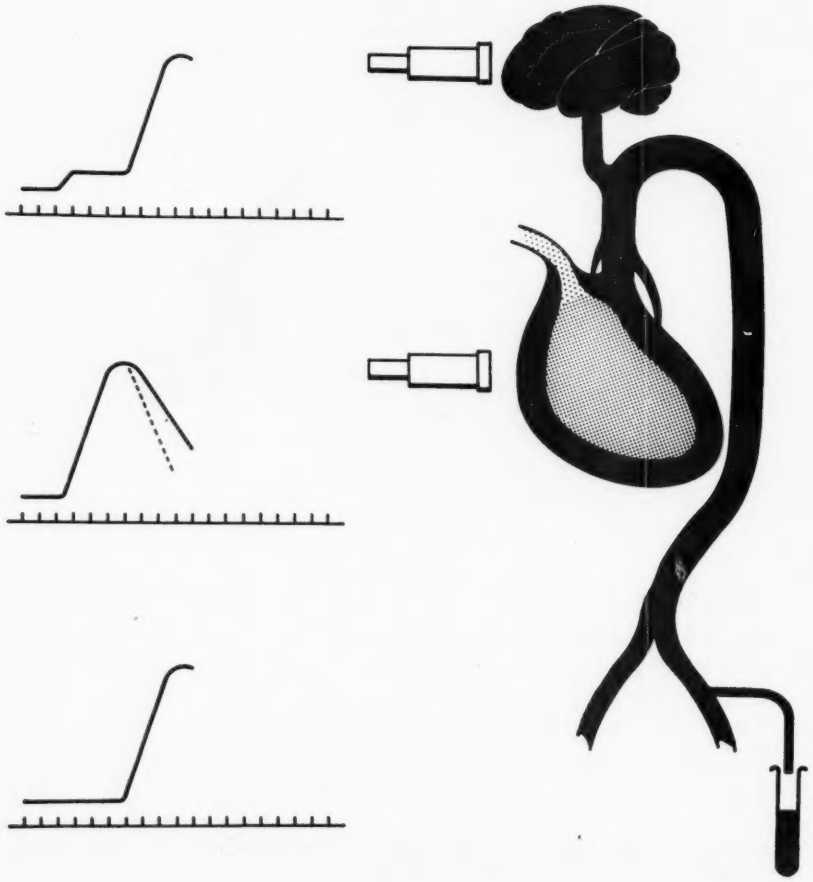

Fig. 3B.

The brain curve is plotted in the same way. During the first 10 to 14 seconds after injection a small rise in counts is detected over the brain due to scatter from the bolus in the thorax. One second before or simultaneously with the beginning of the drop over the heart, radioactivity begins to build up in the brain. At the time the heart has cleared to half value of the peak the brain has built up from 80 to 90 per cent of the ultimate height (4). After a maximum is reached an exponential drop follows. The brain counts from the EPUT meter are plotted as net counts after substracting from each value background plus the increment due to thorax scatter. These brain net counts are plotted and the best straight line for the downslope is drawn.[1] The T ½ is measured and related to the T ½ of the heart as follows. (T½) Heart / (T½) Brain = λ Brain / λ Heart = Coronary Flow Index (CFI). λ = exponential constant.

The counting level observed over the brain has a peak value in a range of 1,800 to 2,500 counts per sampling period, giving a ratio of total counts to background plus scatter of 15 to 20.

In 20 hospitalized patients (in addition to the brain and heart curves) continuous fractional sampling from the femoral or brachial artery was carried out. These individuals were sedated one hour before the test with 200 mg of secobarbital. Novocaine was used as a local anesthesic. Arterial puncture was performed with an 18 gauge needle connected to a polyethylene catheter of 30 cm length with an internal diameter of 2 mm that yielded samples of 0.5-0.6 cc of blood. Arterial sampling was begun at the moment of injection and 40 samples were collected in 53 seconds. The blood samples in pre-calibrated vials were counted in the well-type counter and weighed in an analytical balance. Specific activity in terms of $\mu c \times 10^{-3}$/Gm of blood was determined and plotted on the same graph with the heart and brain curves. Radioactivity appeared simultaneously in the brain and in the femoral or brachial artery. (Fig. 2). The exponentail downslope was determined and the T ½ for the arterial curve measured and compared with the brain downslope (Fig. 5). Figure 3 gives a schematic representation of the curves recorded from the heart, brain and femoral artery during the passage of the radioactive bolus.

CHOICE OF RECORDING INSTRUMENTATION

Two recording devices available for the detection of the heart and brain curves are the rate meter and the EPUT meter. The rate meter is a recording

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[1]Attention should be called to Figure 4 where two different types of brain curves are drawn; the most frequent having one exponential downslope is easily drawn and is similar to the arterial downslope simultaneously sampled. Another type of brain curve is some time observed, *i.e.:* with two exponentials, one very slow that occurs during the first two to four seconds of the downslope, followed by a faster exponential that is in correspondence to the two thirds of the washout segment and that is similar to the arterial downslope. In this case, one cannot draw a single straight line but should work with the tail of the curve or if necessary repeat the measurement. In some patients repeated measurements will show this same phenomenon that could correspond to a certain degree of dephasation of blood flowing to the brain through the different arterial channels.

device with "memory" or smoothing effect for the changing amount of radioactivity to be detected. It consists mainly of a condenser that is very rapidly charged and then discharged at a predetermined speed. The time required for 63 per cent of the discharge to take place is defined as the time constant of the instrument. Time constants range from .05 seconds in super rate meters up to .3 seconds, 2.5 seconds, 10 seconds and 40 seconds in standard instruments. For slowly changing phenomena, instruments with long time constants are adequate, but for rapidly changing processes, such as arterial dilution curves, short time constants of .05 seconds to .5 seconds are required. In order to obtain statistically satisfactory counting error of ± 2 per cent per point with .3 seconds time constant instrumentation and our detection efficiency, doses of 300 μc. to 400 μc of I-131 yield a satisfactory counting level of 1,500 counts per event.

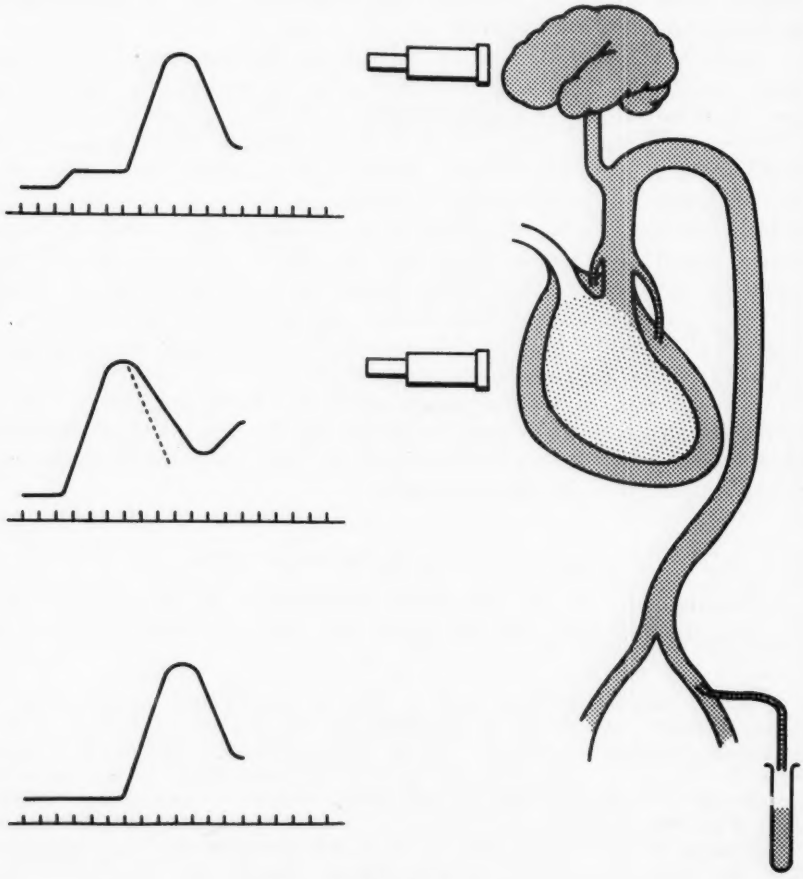

Fig. 3C.

The EPUT meter is an electronic recording device which is, in effect, a digital computer. It adds up all the counts during a predetermined time interval. It can be set to count for periods from 0.1 seconds to 10 seconds. After each time interval it resets automatically, prints the recorded information, and after a display time of 5 microseconds starts counting again. There is absolute independence between the preceding and the following counting period. An optimum sampling period may be chosen that will provide maximal statistical accuracy for each point of the curve with minimal doses of radioactivity. This optimum sampling time is 1 second for the study of dog hemodynamics, and 1.3 seconds for humans. A satisfactory counting rate for the measurement of downslope is achieved by 2000-3000 counts per period at the brain peak level. With a background plus scatter of the order of 200 counts per period the calculated error of a point is $\pm$ 2 per cent.

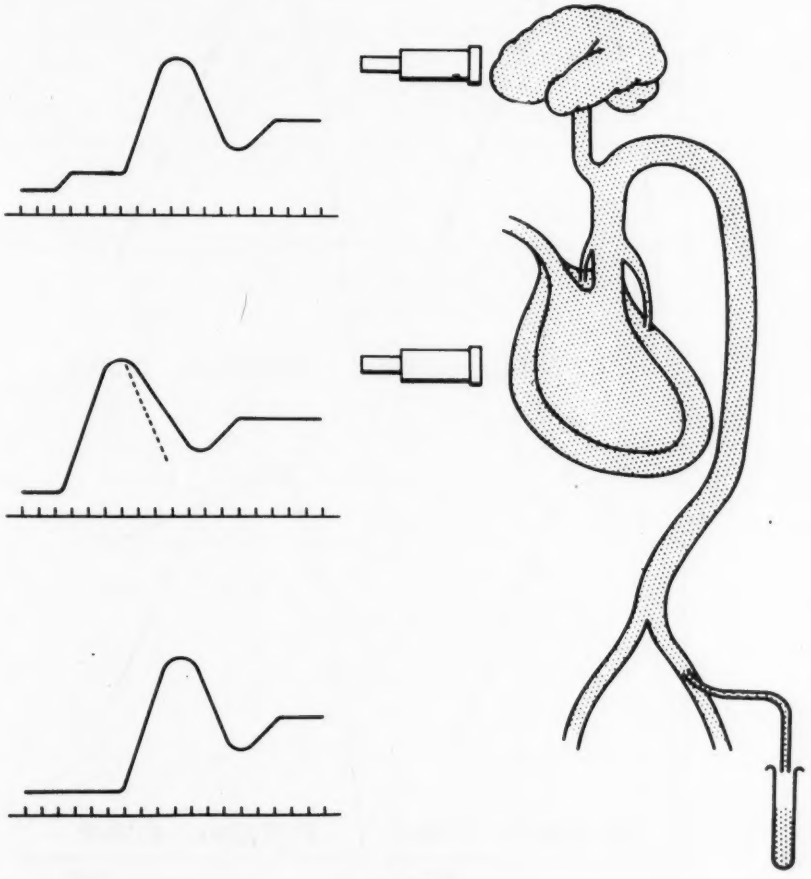

Fig. 3D.

The EPUT meter has the advantage of lengthening the sampling time without introducing lag effects. The administered dose may be 4 to 6 times less than that required by the rate meter. Doses of 60 to 80 μc will provide counting rates of 8000-10,000 counts per 1.3 seconds at the peak of the heart curves. This counting rate provides slopes of calculated error of $\pm$ 1.5 per cent and coronary flow indices of $\pm$ 5 per cent error. (6).

EFFECTS OF COLLIMATION

Higher degrees of collimation will improve the detection of concentration

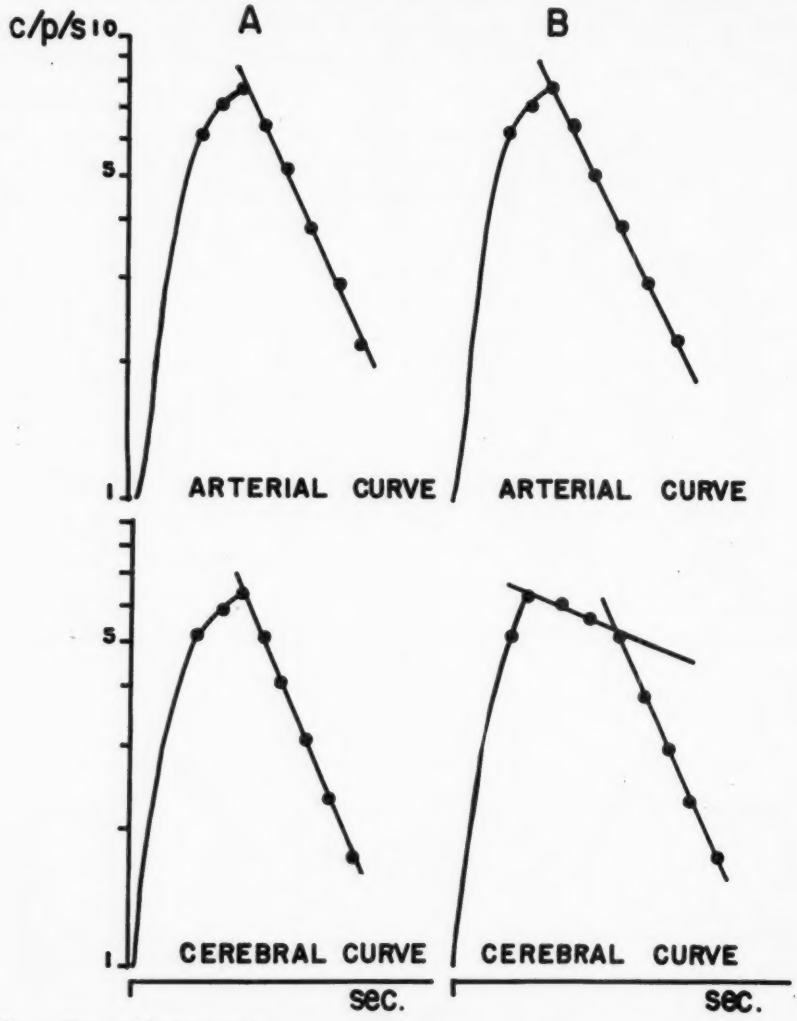

Fig. 4. Types of brain records.

changes through the elimination of the penumbra area as reported by MacIntyre, Pritchard and Moir (7). The counting rate will drop markedly as a price for this achievement. We have found that our degree of collimation is a good compromise, as indicated by the similarity of downslopes in brain and brachial artery curves.

Collimation is to be checked carefully to be certain that both brain and precordial detectors always have the 4 centimeters of collimation. Otherwise different curves will be obtained from those detectors. This can be further checked by placing a point source on a turn table moving at a constant speed and recording the passage of this point source with both detectors placed at the same distance from the turn table. If detectors and equipment are working properly one should record the passage of this point source as identical progressive increasing and later on decreasing radioactivity concentration versus time curves.

RESULTS

In Table II are summarized the results of simultaneous recording of heart and brain curves and femoral arterial sampling in 12 normal subjects and 6 patients with myocardial infarcts. There is close agreement between the downslopes of the brain and arterial curves. The brain T ½ is usually slightly longer than the artery T ½ by a mean factor of 8.1 per cent ± 5 (Fig. 5). Comparison of coronary

TABLE II

DETERMINATION OF CORONARY FLOW INDEX BY SIMULTANEOUS HEART AND BRAIN RECORDING AND ARTERIAL SAMPLING.

	T ½ *Heart*	T ½ *Brain*	T ½ *Artery*	C F I *H/Br.*	C F I *H/Art.*
NORMALS	6.3	4.4	4.2	1.43	1.50
	6.2	4 2	4.6	1.48	1.35
	5 5	3.3	3.0	1.67	1.83
	5.0	3 4	3,1	1.48	1.26
	4.7	2.8	2.9	1.70	1.70
	3.9	2.8	3.1	1 40	1.26
	5.5	2.6	2.7	2.10	2.00
	6.3	4.1	3,7	1.54	1.70
	4.7	2.8	2,1	1.66	2.20
	5.0	3 2	3.1	1.56	1.60
	9.5	5.0	4.7	1.82	1.86
	6.3	4.4	3.9	1.44	1.60
INFARCTS	15 5	12.0	12.0	1.18	1.25
	9.4	8.5	7.8	1.10	1.20
	6.2	5.2	4.2	1.20	1.45
	3.6	3.6	2.6	1.00	1.38
	5.7	5.2	4.2	1 10	1.35
	6.5	6.5	3.4	1 00	1.90

flow indices calculated with arterial T ½ (Fig. 6) or brain T ½ as (Fig. 7) denominator discloses larger values for the coronary flow indices derived from arterial curves (Fig. 6). This agreement indicates that the brain curve can be used as a close approximation of the arterial curve and its T ½ employed as a reliable denominator for coronary flow index. The necessity for arterial puncture is thereby eliminated. Figure 2 illustrates the determination of coronary flow index in a 45 year old normal male.

Observations in additional 59 normal subjects were made employing only heart and brain curves. In 33 normal males the mean coronary flow index with 1.36 ± .16, the observed range was 1.00 – 1.78 (Fig. 9). In 26 normal females, the mean coronary flow index was 1.57 ± .19, observed range was 1.35 – 2.1 (Fig. 9). The coronary flow indices in the various groups are presented in figure No. 9. In 38 patients with myocardial infarction, mean coronary flow index was 1.14 ± .08, observed range 1.00 – 1.37 (Fig. 8).

In 22 normal males a second determination was performed 24 hours later. The mean difference of both determinations was .12 ± .1. In 8 normal females a second determination showed a mean difference of .13 ± .09. In 25 infarcts patients the mean difference was .08 ± .06.

In 10 patients with myocardial infarcts measurement was performed three

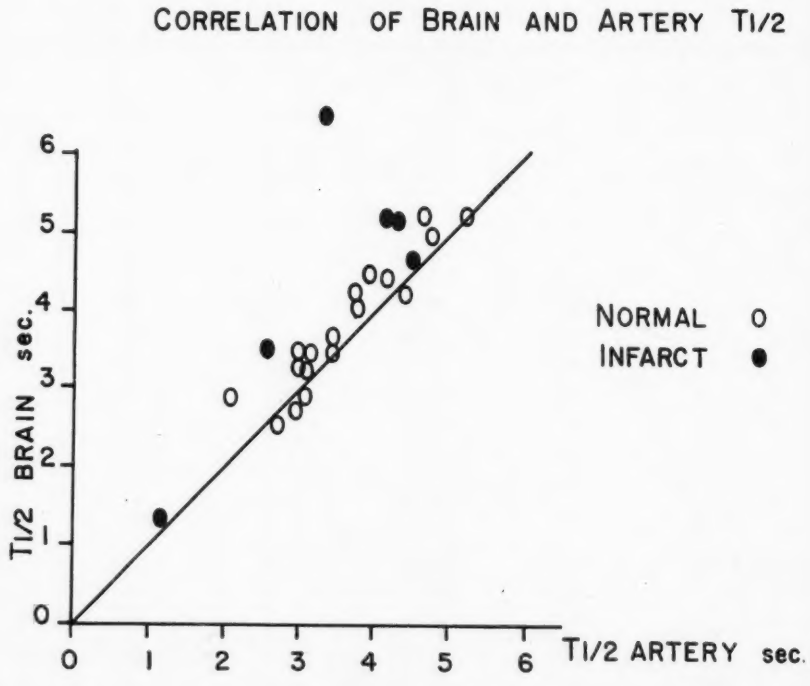

Fig. 5. Correlation of brain and artery T ½.

and seven days after administration of .75 milligrams of reserpine[1] given orally daily. No significant difference was observed upon subsequent determinations. Results are shown in Figure 10. In the 7 normal individuals with abnormally low coronary flow index, the subsequent determination after reserpine given in the same way shows a significant increase back to normal range as shown in Figure 10.

Table I shows the distribution of coronary flow index of normal and myocardial infarction patients in terms of age.

An analysis of coronary indices of infarction patients was performed. No significant difference was found between old and new infarcts and between anterior or posterior wall infarction. The variation of the method upon subsequent determination is such that no significant conclusion can be drawn from values distributed in the coronary range.

In 62 patients cardiac index was calculated from the brain curve, and no correlation was apparent.

DISCUSSION

It is striking that coronary flow indices in our series of patients with myocar-

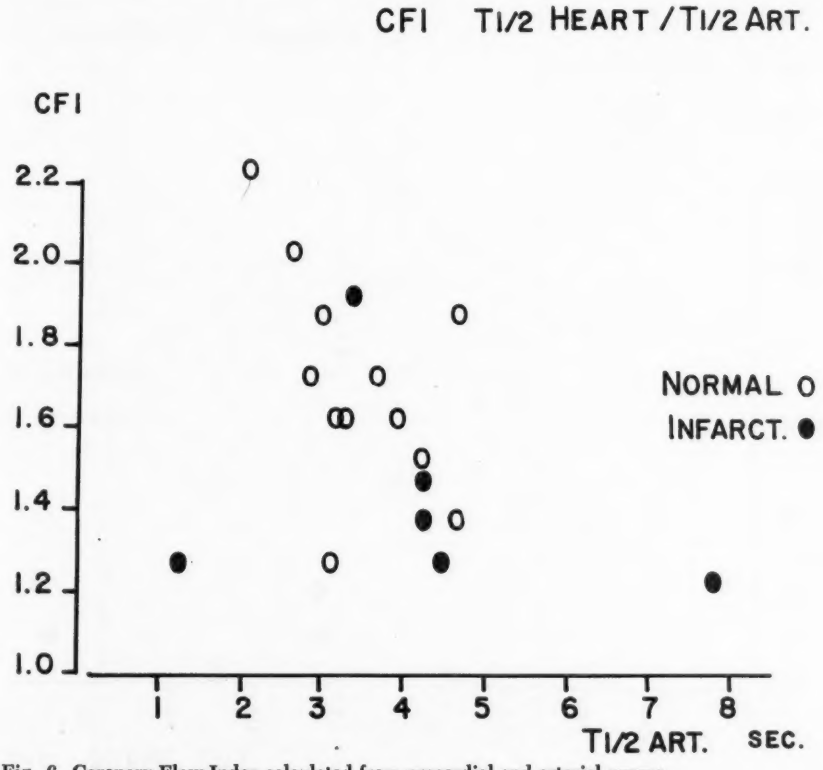

Fig. 6. Coronary Flow Index calculated from precordial and arterial curves.

[1]Reserpine supplied by CIBA Laboratories, Santiago, Chile.

dial infarction fall within a narrow range that almost does not overlap the indices obtained in the series of subjects having no clinical evidence of coronary disease. Two patients with coronary flow indices of 1.35 had myocardial infarction, three and seven years before. At the present time they are asymptomatic and show normal electrocardiograms. The findings suggested that the coronary flow index may be a useful test for the detection of coronary disease. On the basis of present experience diagnostic sensitivity seems to be at least as reliable as the electrocardiogram because, of 38 patients with electrocardiographic evidence of coronary disease, only two had a coronary flow index above 1.2. The wide range of coronary flow index value found in the non-coronary subjects suggest that the entire group cannot be considered normal. All but three women were premenopausal and their coronary flow index values were in the higher range of the group 1.35 – 2.1. One 21 year old girl had a CFI of 1.17. Perhaps the true normal coronary population could be derived only from these premenopausal females free from hypertension, endocrinopathies or hypercholesterolemia.

The non-coronary group of patients with the low indices is composed mainly of males of 30 to 40 years of age. The young individuals who appeared in this group might be suspect of potential coronary disease. Six of them showed values

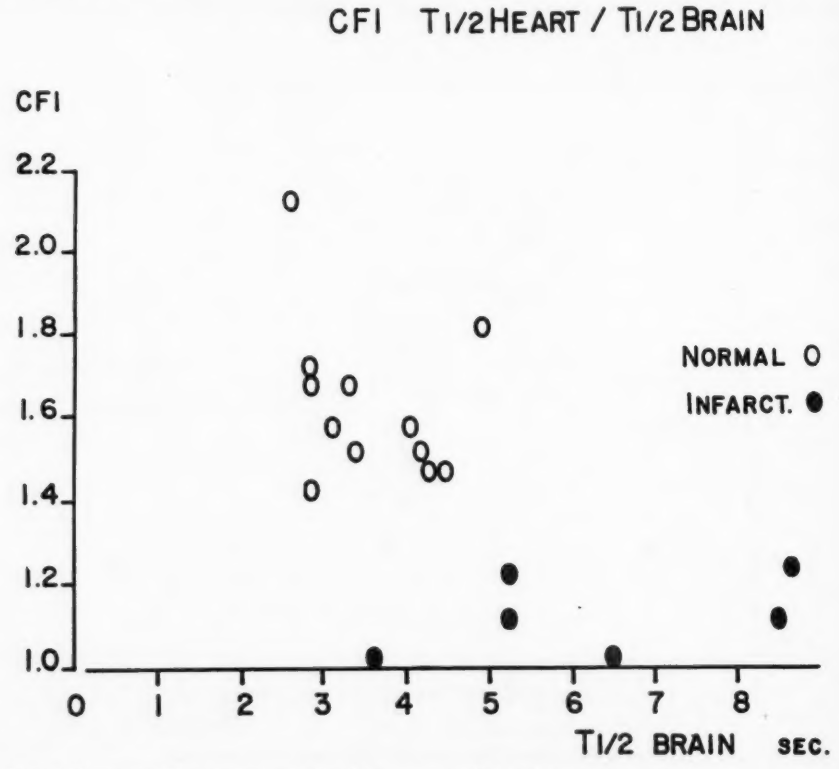

Fig. 7. Coronary Flow Index calculated from precordial and brain curves.

within the coronary range, 1 — 1.2. It appears highly important that young individuals with coronary flow indices below 1.3 be followed carefully and perhaps studied with other diagnostic methods in order to define the significance of their suspiciously low coronary flow indices. It is particularly remarkable that this group of patients improve their coronary flow index after administration of reserpine, while patients with myocardial infarction do not show changes in this parameter after administration of the drug.

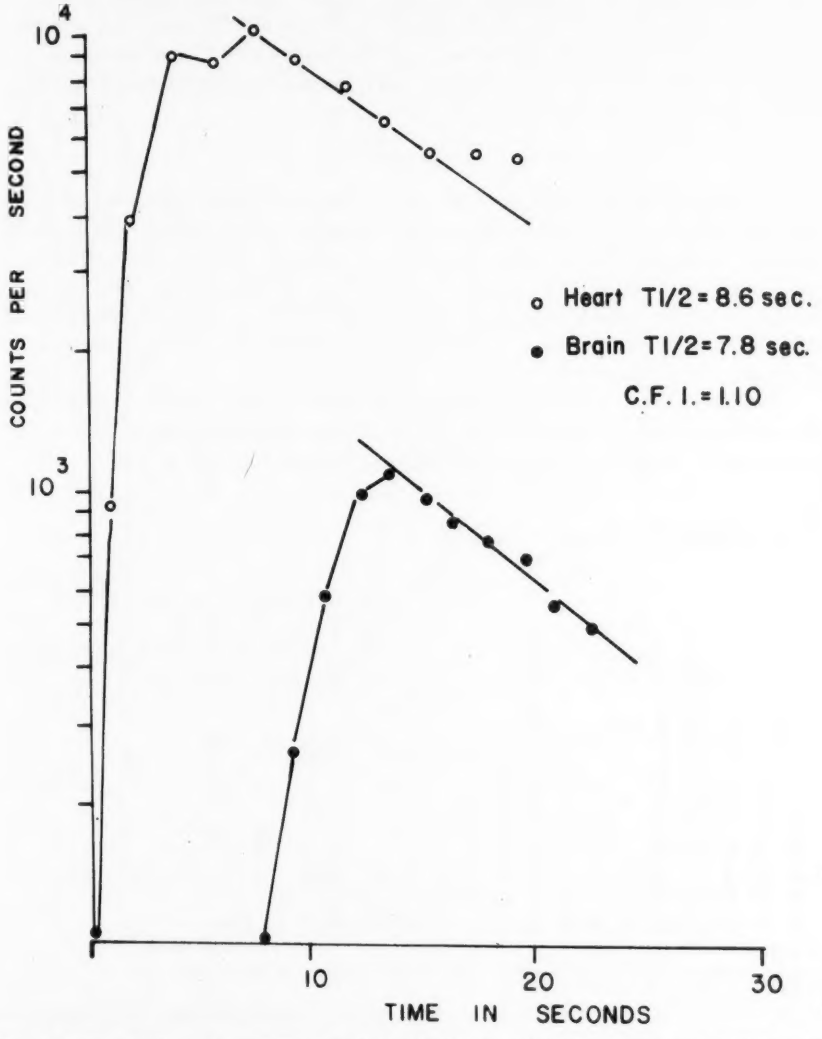

Fig. 8. Determination of coronary flow index by heart and brain curves in a patient with myocardial infarction.

CFI calculated from heart and arterial curves show more ovelap (Fig. 6). Others have observed larger degrees of overlapping between normal and coronary patients when working without sedation at higher levels of Cardiac Output (12). It is known from Ketty *et al.* (13), that cerebral blood flow remains constant over a wide range of physiological conditions, and Nylin (14) has reported that arterial dilution curves are minimally distorted by passage through the brain; thus it may be, that the brain is a good image of the artery at normal levels of Cardiac Output, while the very sharp curves of high Cardiac Output could be prolonged by cerebral circulation, thus distorting the recorded dilution curves.

When RISA is employed as the indicator, the amount of total body radiation delivered by one determination of coronary flow index in a 70 Kg individual is in the order of 150 millirads (11). The method is, therefore, radiologically safe, technically simple, and repeatable.

SUMMARY

1) Normal subjects and patients with coronary disease were studied by simultaneous detection of the passage of a radioactive bolus through the heart, the brachial or femoral artery, and the brain. In normal subjects the arterial and brain curve downslopes are similar to each other and are steeper than the heart downslopes. The delay in the heart downslopes is due to coronary radioactivity interposed between the heart cavities and the detector. In coronary patients the three downslopes are similar.

2) T ½ Heart / T ½ Brain is defined as Coronary Flow Index (CFI). In 33 normal males mean CFI is 1.36 ± .16, in 26 normal females mean CFI is 1.57 ± .19 and in 38 patients with myocardial infarction mean CFI is 1.14 ± .08.

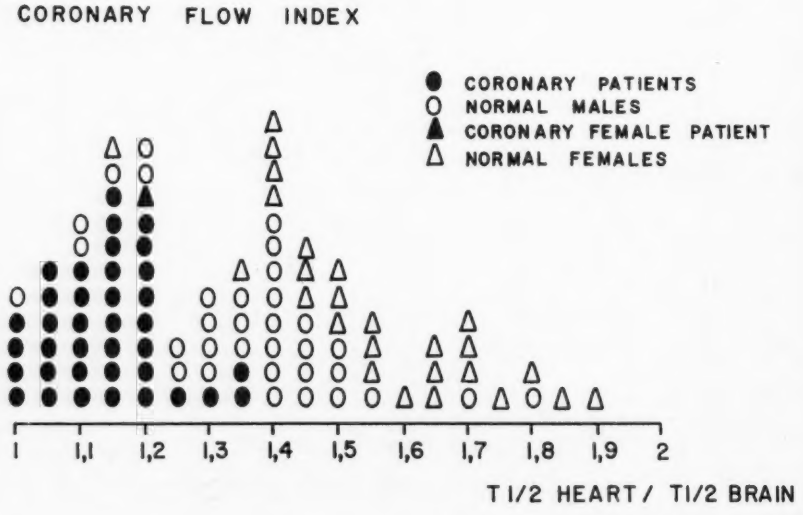

Fig. 9. Determination of Coronary Flow Index by precordial and brain recording.

3) In seven normal individuals with abnormally low CFI subsequent determinations after administration of reserpine were normal. No modification was recorded in infarct patients.

4) These clinical observations are in accord with the experiments in animals and theoretical analyses which demonstrate that the ratio of these downslopes is an index of coronary blood flow.

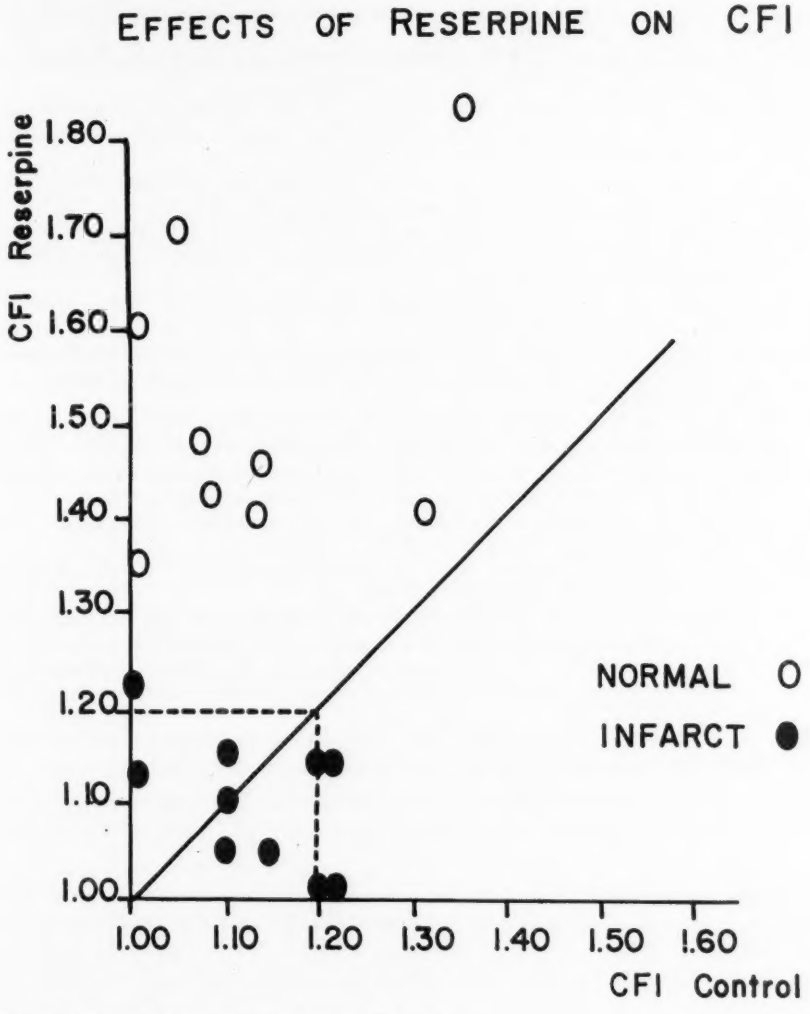

Fig. 10. Effects of Reserpine on Coronary Flow Index.

ACKNOWLEDGMENTS

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Production and Use of Iodine-125[1]

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Reports from this (1,2) and other (3) laboratories have suggested that there may be some advantages in substituting iodine-125 for iodine-131 in a number of clinical and experimental situations. Among these advantages are the longer half-life of iodine-125 (60 days) which results in a greatly increased shelf-life of tagged compounds, and the lower energy of its radiations which reduces shielding requirements and permits more efficient detector design. These factors allow enhanced counting efficiency and scanning resolution, and, together with the absence of β-radiation, lead to decreased radiation dosage and increased tolerable isotope dosage. The availability of the isotope, however, has been greatly limited because production in the cyclotron from tellurium (3,4), even when enriched target material is used, results in heavy contamination with the undesirable 13-day I^{126}, making the resultant product unsuitable for human and experimental use to a considerable extent. Purification of the I^{125} by allowing the I^{126} to decay results in loss of much of the I^{125}, thus increasing the cost. The purpose of the present report is to describe our work on production of I^{125} as a daughter product from the neutron activation of xenon-124 to xenon-125, and to report the preliminary results of several practical applications.

PRODUCTION METHODS

The high, 74 barn cross section of xenon-124 reported by Tobin and Sako (5) made the production of relatively pure I^{125} in large quantities by the $Xe^{124}(n, \gamma)Xe^{125} \xrightarrow[18\ hr]{EC} I^{125}$ reactions appear quite feasible, even though the natural abundance of Xe^{124} is only 0.094 per cent. However, several samples of xenon irradiated in the A.N.L. CP-5 reactor were found to be contaminated with substantial amounts of I^{126}. Samples of carrier-free I^{125} separated from the irradiated xenon were further exposed to the neutron flux in the reactor and this

[1]From the Argonne Cancer Research Hospital, operated by The University of Chicago for the United States Atomic Energy Commission, and the Departments of Surgery and Radiology, The University of Chicago, Illinois.

TABLE I

PILE NEUTRON ACTIVATION CROSS SECTIONS
(BARNS)

Target	$\sigma_a Xe^{124}$	$\sigma_a I^{125}$
Xe^{124}	169	—
Xe^{124}	179	—
Xe^{124}—I^{125}	173	1160
Xe^{124}—I^{125}	175	1138
I^{125}	–	1180
I^{125}	–	1110

also resulted in production of I^{126}. The effective neutron activation cross sections calculated from these various experiments for the $Xe^{124}(n, \gamma)Xe^{125}$ and $I^{125}(n, \gamma)I^{126}$ reactions are shown in Table I. The identical cross section value which is obtained by activating I^{125} alone or in the presence of xenon indicates that no reaction other than $I^{125}(n, \gamma)I^{126}$ contributes significantly to the production of the I^{126}.

The fact that xenon-124 is first activated to xenon-125 and then decays with an 18-hour half-life to I^{125} makes it possible to eliminate the formation of I^{126} to a large extent by activating a large quantity of xenon for a short time. Also, since the formation of I^{126} is a second order process, the per cent contamination is proportional to the flux, and with a low flux and a long irradiation time large and relatively pure amounts of I^{125} may be produced. In Table II are shown representative yield computations for these two methods.

For irradiation, the xenon was contained in a thick-walled irradiation vessel of Zircaloy 2 (Fig. 1). This container was first evacuated and then loaded by freezing the xenon gas (about 3 liters at S.T.P.) into the chamber using liquid nitrogen, which resulted in an internal pressure of approximately 1,500 lbs/in^2 at

TABLE II

I^{125} PRODUCTION FROM PILE NEUTRON ACTIVATION (0.1 MOLE XENON)

$$Xe^{124} \xrightarrow[\sigma = 174 \text{ barns}]{n,\gamma} Xe^{125} \xrightarrow[18 \text{ hr.}]{EC} I^{125} \xrightarrow[\sigma = 1145 \text{ barns}]{n,\gamma} I^{126}$$

.094%

	Method 1	*Method 1A*		*Method 2*
Thermal Neutron Flux (n/cm.^{2}/sec.)	6×10^{13}	6×10^{13}		6×10^{12}
		In Pile	Out of Pile	
Irradiation Time	3.5 days	7 days	26 days	30 days
Yield of I^{125}	615 mc.	1200 mc.	⟶ 900 mc.	450 mc.
Contamination with I^{126}	2%	6%	⟶ 2%	2%

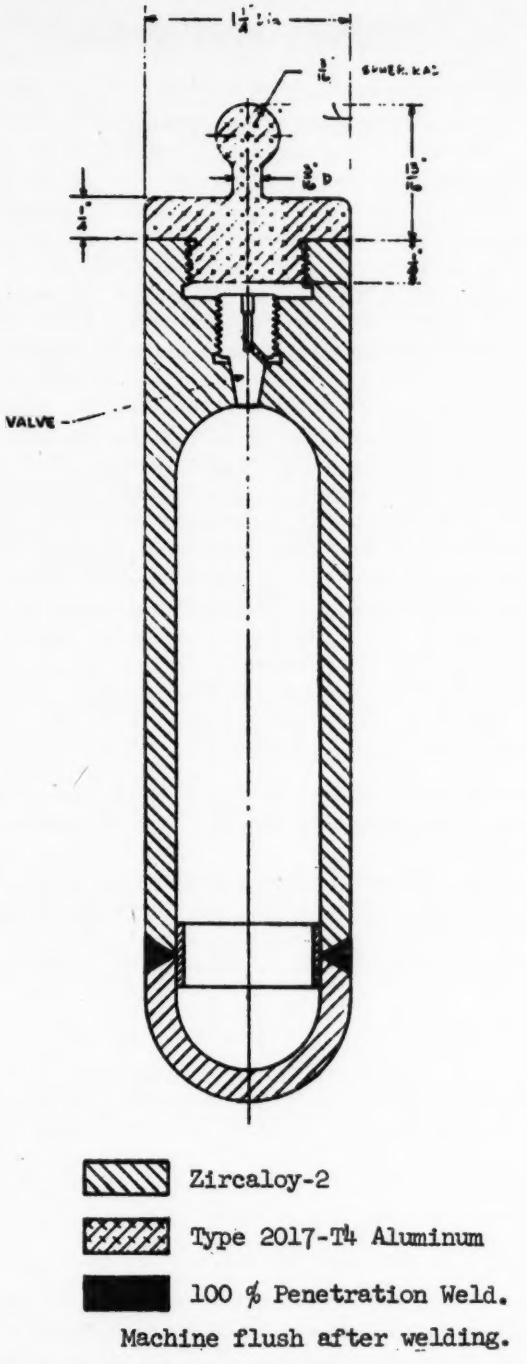

Fig. 1. Zircaloy-2 irradiation vessel for xenon. Volume 35 ml, contains 16 g xenon at 1500 lbs/in², 90° C.

TABLE III

CADMIUM RATIOS (40 MIL)*

$Xe^{124} \longrightarrow Xe^{125}$	$I^{125} \longrightarrow I^{126}$	$Co^{59} \longrightarrow Co^{60}$
3.05	4.22	13.8

*Cadmium ratio $= \frac{\text{activity induced in unshielded sample}}{\text{activity induced in cadmium-shielded sample}}$ The cadmium shield eliminates the thermal neutron flux, and allows the epithermal neutrons to pass.

the temperature of the reactor. Flux depression inside the loaded pressure vessel as measured with cobalt monitors was 7 per cent. The activated sample was allowed to sit for several days following removal from the reactor, in order to permit the xenon-125 to decay to I^{125}. The irradiation vessel was then cooled to the temperature of liquid nitrogen to freeze the xenon, the valve opened, and the vessel warmed in a dry-ice acetone bath to evaporate the xenon into a previously evacuated storage vessel from which it could be later re-introduced into the irradiation vessel for a second irradiation. It is necessary to contain the xenon because approximately one hundred curies of various radioactive xenons are produced. The carrier-free I^{125} remained in the irradiation vessel from which it could be almost completely removed with three washings of 0.1 per cent potassium bisulfite adjusted to pH 7-8 with potassium hydroxide. Each washing was allowed to stand in the vessel for several hours. Small quantities of cesium-137 produced from xenon-136($Xe^{136}(n, \gamma)Xe^{137} \xrightarrow{\beta} Cs^{137}$) were removed by pouring the bisulfite solution containing the iodine activity through a small acid phase Dowex-50 column.

Because all these experiments were carried out in the high flux region of the reactor where the epithermal flux is high, and because the observed neutron activation cross section of the xenon-124 was approximately twice that of the reported value, a sample was irradiated in the isotope tray where the flux is well moder-

TABLE IV

I^{125} DECAY SCHEME PARAMETERS

Quantity	*Symbol*	*Value*
Physical Half Life	T_p	60 days
Fraction of Disintegration by K-Capture (9)	K	$.813 \pm .02$
Fraction of Disintegration by L-Capture (9)	L	$.187 \pm .02$
Fraction of γ's Unconverted (10)	γ	$.07 \pm .02$
Fraction of γ's Converted in K Shell (10)	C_k	$.80 \pm .05$
K Fluorescence Yield (11)	ω_k	.855
Total K and γ Photons/Disintegration	$K\omega_k + C_k\omega_k + \gamma$	$1.45 \pm .05$

ated (cobalt cadmium ratio ~ 1,000.) The observed activation cross section of xenon-124 under these circumstances was 94 barns, which more nearly approximates that of the reported value. The large neutron resonance absorption of xenon-124 at 5.16 ev (6) should account for this difference. The cadmium ratios of xenon-124 and I^{125} were measured in the hope that I^{125} might be produced in significant quantity without production of I^{126} by activation of cadmium-shielded xenon. The results of one experiment are shown in Table III. Unfortunately, however, the I^{125} also appears to have a high resonance absorption so that this approach results in little improvement. The thermal neutron activation cross sections calculated (7,8) from these data are 115 barns for Xe^{124} and 890 barns for I^{125}, with resonance activation integrals of 1210 barns and 6500 barns respectively.

I^{125} decays with a 60-day half-life by electron capture to the 0.0354 mev excited state of tellurium-125, which then decays by emission of a gamma which is largely converted in the K shell. The significant physical parameters of the decay scheme are shown in Table IV. Since the net result of the decay by these modes is the production of two coincident photons with energies of 27.3 to 35.4 kev, it is possible by conventional reasoning to develop a formulation for a coincidence method assay in terms of the abundances of the various photons involved (Eq. 1).

$$\text{Eq. 1. } A = \frac{N_t^2}{N_c} \times \frac{K\omega_k\,(\gamma + C_k\omega_k)}{(K\omega_k + \gamma + C_k\omega_k)^2}$$

A = Activity
N_c = Total coincidences detected
N_t = Total photons detected (1 coincidence = 2 photons)

This expression is quite insensitive to uncertainties in the decay scheme parameters and may be greatly simplified by an approximation (Eq. II).

$$\text{Eq. II} \qquad A = \frac{\left(\frac{N_t}{2}\right)^2}{N_c}$$

which involves an error of approximately 0.1 per cent. The coincident photons may be detected with great ease by the crystal summing technique (12), using a multichannel analyzer, as shown in Figure 2, or integral bias counting, as shown in Figure 3. This assay method was used in all the above-mentioned cross section determinations.

DETECTOR DESIGN AND DOSIMETRY

In considering detector design for I^{125}, the low energy of the emitted photon radiation makes necessary very radical differences in the shielding requirements. Because virtually complete shielding is obtained with 2 to 3 mm of lead, collimators may be designed with paper-thin septa which thus increases the counting

efficiency by a factor of three or more (13). A crystal of thallium-activated sodium iodide 2 mm thick will give virtually complete absorption of the radiation and only a negligible escape peak, since almost all the radiation is below the iodine K edge (see Fig. 2). The absorption is almost exclusively photoelectric, so that the interaction ratio and photo-fraction both approach 100 per cent. The attenuation

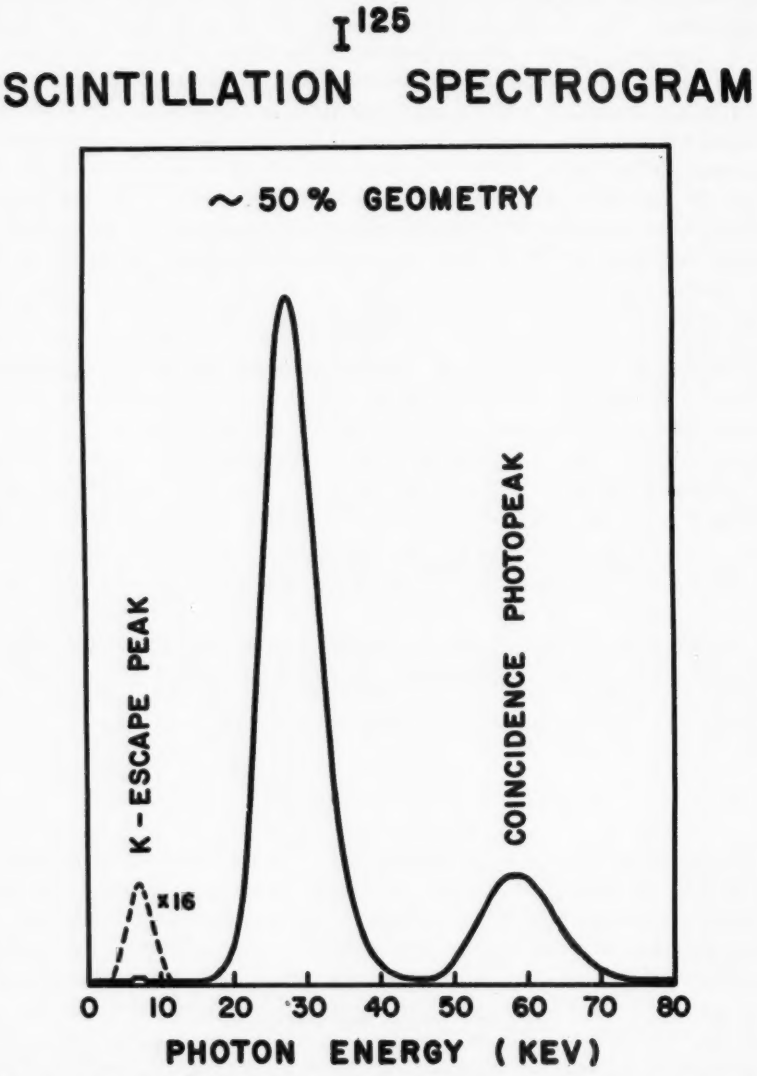

Fig. 2. Scintillation spectrogram of I^{125}, using a 2-mm thick NaI crystal with Be window at ~ 50 per cent geometry. The very small escape peak from the unconverted 35.4 kev γ ray is visible. The principal photo peak at ~ 30 kev includes the Kα, Kβ and γ photons, and the smaller peak at ~ 60 kev represents coincidences.

TABLE V

I^{125} K AND γ PHOTONS

	Photons per Disintegration	*Fraction of Total*	*Kev/Photon*	*Kev/Disintegration*	*r/mc-hr at 1 cm*	*Calc. HVL* Tissue Equiv.*
Kα	1.09	.75	27.3	29.8	1.03	1.82 cm.
Kβ	.29	.20	31.2	9.0	.21	2.16 cm.
γ	.07	.05	35.4	2.5	.04	2.56 cm.
Total	1.45	1.00	—	41.3	1.28	1.92 cm.

*Density 1 tissue equivalent material (15).

of the radiation in the 5-mil window of the commercially available Be window crystals is less than 1 per cent. The use of such a small crystal has the additional advantage of a greatly reduced background from cosmic radiation and other extraneous ambient activity.

In considering the dosimetry of I^{125}, the available energy to produce ionization which is released per disintegration, assuming 81.3 per cent K-capture and 18.7 per cent L-capture is equal to the weighted sum of the energies of the two resultant excited states of tellurium, plus the 35.4 kev energy of the gamma transition. Much of the energy appears as conversion electrons, Auger electrons, and the very low energy L and M, etc. photons, which for practical purposes in tissue may be treated as β-like radiations in that they are absorbed very close to their point of origin. The other radiations, tellurium Kα and Kβ radiations, and the unconverted gamma radiation make up the gamma-like radiations (see Table V and VI). The quantity of the β-like energy which is dissipated per disintegration may be obtained by subtracting the energy of the gamma-like radiation from the total available energy. This amounts to 21.0 kev per disintegration of β-like radiation, and 41.3 kev per disintegration of γ-like radiation. Comparison of the dosage from I^{125} and I^{131} for three situations is shown in Table VII.

TABLE VI

I^{125} ENERGY PER DISINTEGRATION AVAILABLE FOR IONIZATION

γ Transition	35.4 Kev.
K-Capture	26.0 Kev.
L-Capture	.9 Kev.
Total	62.3 Kev.
K and γ Photons	41.3 Kev.
Conversion and Auger Electrons Soft Fluorescent Photons (β-like)	21.0 Kev.

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TABLE VII

I^{131} AND I^{125} COMPARATIVE RADIATION DOSAGE (APPROXIMATE)

	Average Dose rads/μcd/gm											
	I^{131}				I^{125}			I^{131}		I^{125}		
Organ	*β*	*γ*	*Total*	*β-Like*	*γ-Like*	*Total*	*Procedure*	*Initial Dose Rate*	*Total Dose*	*Initial Dose Rate*	*Total Dose*	*Dose I^{131}/I^{125}*
								Teff = 6.9 d		Teff = 27 d		
30 gm Thyroid	110	10	120	92	38	130	Radioiodine Scan 50 μc 60% uptake T biol = 50 days	10.4 rad/d	103 rad	1.5 rad/d	58 rad	1.78
1500 gm Liver	110	42	152	92	100	192	Rose Bengal Scan 200 μc T biol = 2 hrs	Teff = 2 hrs. 74 m rad/hr	210 m rad	Teff = 2 hrs 12.4 m rad/hr	35 m rad	6.0
70 Kg Total Body	110	90	200	92	180	272	Blood Volume Tagged Albumin 5 μc T biol = 17 days	Teff = 5.4 d 1.3 m rad/d	10 m rad	Teff = 43 d .23 m rad/d	14 m rad	0.7

The half-value layer for the I^{125} radiations measured in density 1.00 tissue equivalent solution (14) using narrow beam geometry was 1.99 cm, which agrees very well with the calculated value of 1.92 cm. The wide beam half-value layer observed for the same medium was 2.53 cm. This difference is due to the scattered radiation. When the tissue which the radiation is traversing is fatty, the HVL is somewhat greater.

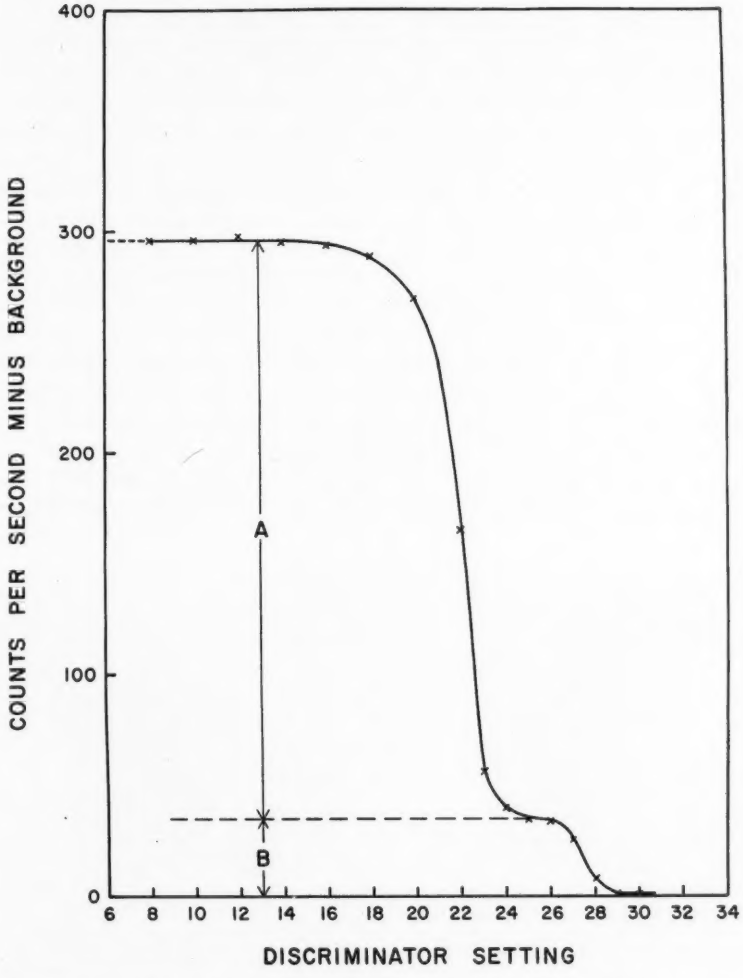

Fig. 3. Detector and source as in Figure 2. Observations are displayed as an integral bias curve. *A* represents area of the principal photo peak and *B* the area of coincidence peak.

SCANNING APPLICATIONS

In the light of this discussion the substitution of I^{125} for I^{131} for thyroid scanning should give, under ideal circumstances, approximately 10 times as many detectable photons per unit of radiation dosage to the patient, or, conversely, the gland could be scanned with one-tenth the radiation dosage produced by I^{131}. An additional factor is present when one considers the use of radioactive iodine to demonstrate "cold nodules" in either the thyroid or liver. In this situation the normal tissue takes up the iodine tag, while the "cold nodule" does not, which makes it appear as a void in the scan. A cold nodule on or near the surface of the organ appears with greater contrast when I^{125} is used because the soft radiations from the underlying tissue are absorbed in the nodule, whereas the strong γ-radiations from I^{131} pass through. In this situation statistically significant differences in count rates may be observed with lower over-all count rates, and, consequently, an additional improvement in resolution is obtained. It can be shown that for the same radiation dosage and scanning time, a nodule on the surface of the liver one-half or less of the size detectable with I^{131} should be detectable with I^{125}, using optimal collimators (13). Since nodules below the surface of the liver are not as readily detectable as with the penetrating radiation of I^{131}, some information is lost (14), in return for a better look at the surface of the organ.

Using the design features mentioned above, scintillation probes for the detection of I^{125} are under construction in our laboratory. However, it has been found possible to use unmodified commercial scanning equipment (16) substituting I^{125} for I^{131} μc for μc. About 40 per cent of the count rate is lost due to absorption in the aluminum can of the crystal. Using such equipment, comparative scans between I^{125} and I^{131} are shown for the liver and thyroid in Figures 4

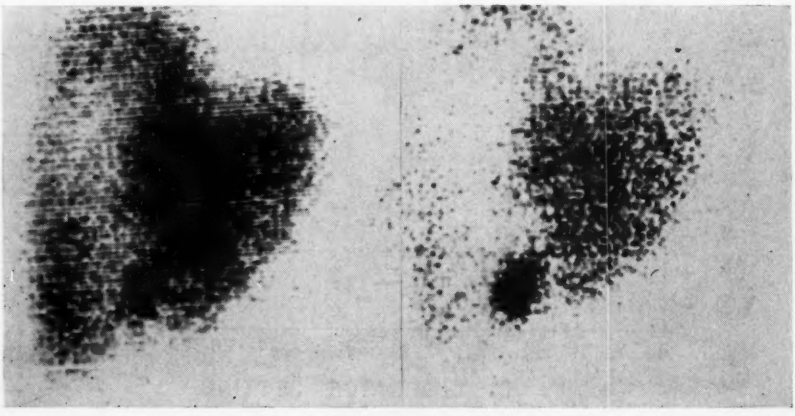

Fig. 4. Rose Bengal photoscans of liver using available commercial equipment showing results obtained with 200 μc of I^{131}, on left; and with 200 μc of I^{125}, on right. Note the marked increase in contrast of the metastatic tumor nodules visible with I^{125}.

and 5. I^{125} and I^{131} scans of the liver show the marked increase in contrast in cold metastatic tumor tissue and the I^{125} thyroid scan is of at least equal quality to that using I^{131}. Thus, the advantages of using I^{125} appear to be great enough to justify the substitution of this material for I^{131} in routine scanning procedures even without special detection equipment. Even though the dose per μcd/gm of tissue is approximately the same for both isotopes, the fact that I^{131} decays to a considerable extent before a great quantity is excreted, and that I^{125} is to a considerable extent excreted before it has a chance to decay, results inevitably in less of a radiation dosage when I^{125} is substituted for I^{131} μc for μc, except under the most unfavorable circumstances. Stated differently, the energy dissipation rate per μc is much less with I^{125} so that in applications requiring short exposures, such as Rose Bengal liver scans, there is greatly reduced relative exposure from I^{125}.

The fact that I^{125} radiations have a half-value layer of 2 to 2½ cm in tissue virtually precludes this material from the measurement of absolute quantitative uptake in the thyroid gland. Variation in the thickness of the overlying tissues and the impossibility of constructing a special identical phantom for each patient, make necessary the use of an isotope with more penetrating radiation for this particular application when using ordinary counting methods. It should be possible, however, to determine the clearance on some related parameter since the shape of the uptake curve would not be altered by attenuation. Tissue attenuation of course precludes the use of I^{125} for brain scanning. I^{125} is ideally suited for tests in which small *in vitro* samples are counted, as in blood volume measurements or T3 absorption tests. Such small samples in plastic test tubes may be counted with about 50 per cent efficiency in conventional well counters having the standard 30-mil aluminum lining. In experimental applications, the low energy Auger and conversion electrons of I^{125} may be counted in windowless proportional flow counters, also with about 50 per cent efficiency. The low energy electrons

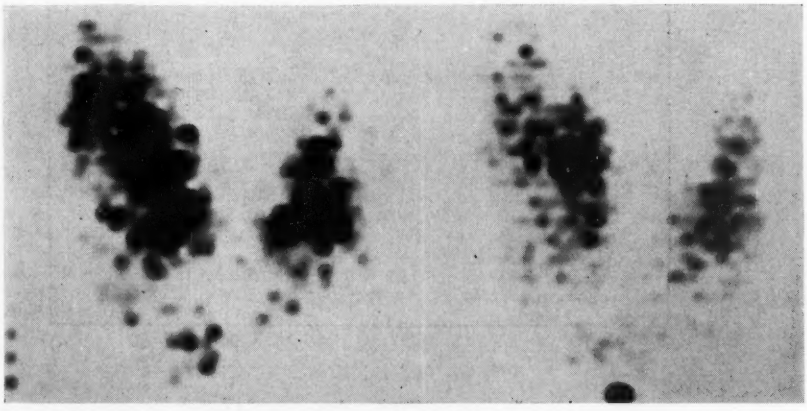

Fig. 5. Photoscans of thyroid using same equipment as in Figure 4 with 50 μc of I^{131}, on right; and 50 μc of I^{125}, on left.

may be also used to make very high resolution radio-autographs comparable to tritium and the use of I^{125} for long-term metabolic studies in thyroid physiology is demonstrated in Figure 6.

SUMMARY

The procedures for production of I^{125} by neutron activation of xenon in relatively pure form are outlined. The pertinent dose calculations for the use of I^{125} in thyroid and liver scanning are presented, and the advantages of I^{125} from

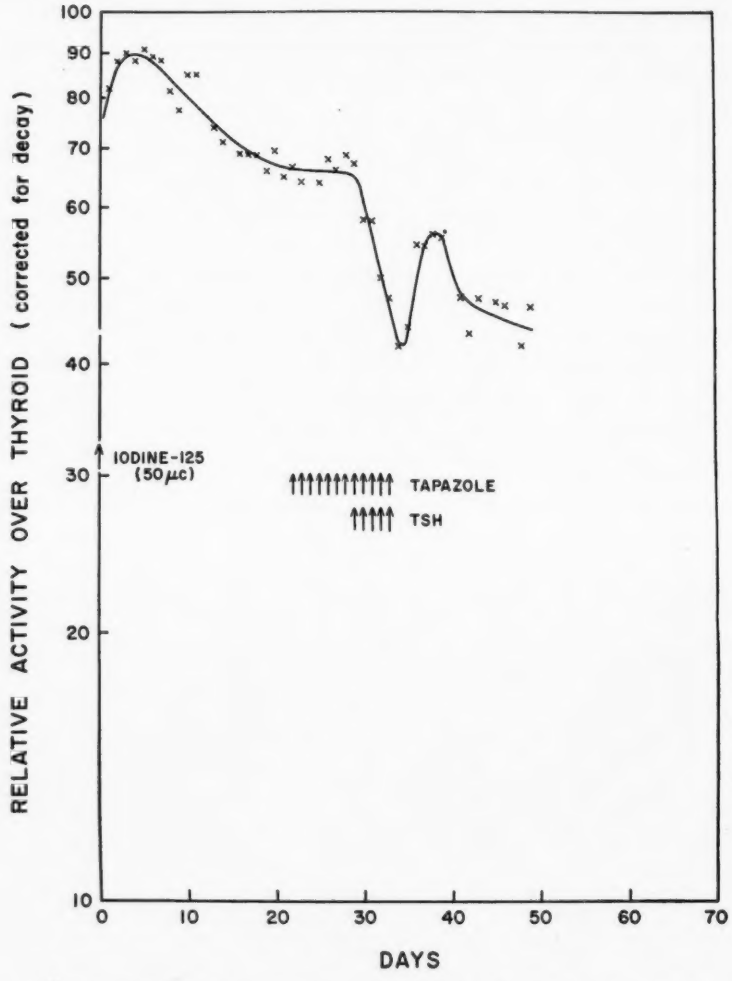

Fig. 6. Attempt to influence the excretion of I^{125} by administration of Tapazole and thyroid-stimulating hormone in a euthyroid patient, BMR -2, PBI 6.8.

the point of view of long half-life, increased tolerable isotope dosage, reduced radiation dosage and improved scanning resolution are illustrated. While many of these advantages cannot be fully exploited without special detectors, they appear to be great enough to justify the substitution of I^{125} for I^{131} in many instances using available commercial detection equipment.

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ANNOUNCEMENT

The Medical Division of the Oak Ridge Institute of Nuclear Studies will present the Eighth ORINS Symposium in Medicine October 21-25, 1963. The topic will be "Progress in Dynamic Clinical Studies with Radioisotopes." Speakers will be invited authorities from throughout the United States and selected guest experts from Europe.

Clinical topics will include renograms, cardiac shunt detection, cephalic blood flow, cardiac output, coronary flow, lymph flow, clearance procedures, pulmonary function, copper turnover, albumin turnover and others. There will also be basic topics on new instruments for flow metering, limits of rate meter recording, kinetic theory in nuclear medicine, analysis of multi-compartment systems and turnover.

Co-chairmen are Ralph M. Kniseley, Medical Division, ORINS, and W. N. Tauxe, Mayo Clinic, Rochester, Minnesota. Eligible participants are physicians and paramedcal personnel with previous experience in radioisotope procedures. Enrollment is limited. Application forms can be obtained from:

Ralph M. Kniseley, M.D.
Medical Division
Oak Ridge Institute of Nuclear Studies
Oak Ridge, Tennessee

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A Query Into the Use of Tracer Doses of I-131

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Boston

INTRODUCTION

Much public concern has been expressed over the hazards to man from ionizing radiation. Many studies (1,2) have confirmed that the medical uses of radiation constitute the largest man-made source of exposure. Except for one report, (3) relatively little attention has been paid to an assessment of the use of radioactive isotopes.

There have been approximately 2500 medical isotope licenses issued by the Atomic Energy Commission. No central record is kept of the amounts of radioactive materials used by these licensees, the ways in which the isotopes are administered, or the types of patients who receive them. This information might prove valuable not only from the health assessment viewpoint, but also as a possible basis for future epidemiological investigations.

The use of tracer doses of I-131 for evaluation of thyroid gland status was selected for study for several reasons. Firstly, previous estimates had indicated that this utilization accounts for the majority of administrations of isotopes in this country. (3) Furthermore, it was believed that the information would be more complete and easier to collect if the scope of the study were limited to one isotope and the characteristics of the individual patients who received the isotope. Lastly, as the child's thyroid is thought to be a sensitive organ to the deleterious effects of radiation, it was hoped that a suitable population group for epidemiological study might be found.

Twenty-four major medical teaching hospitals with whom previous contacts had been made, and where information on the use of I-131 was known to be readily available in a central thyroid clinic were asked to participate. Their location is shown in Table I. It is obvious that these hospitals are not representative of the United States, or even of the city of their location, and that they do not represent a random sample.

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[1]Department of Radiology, Massachusetts General Hospital; formerly, Director, Medical X-ray Research and Development Laboratory, Division of Radiological Health, United States Public Health Service.

These centers were asked to fill out a simple questionnaire (Fig. 1) at the time of each administration of a tracer dose of I-131 for evaluation of the thyroid gland during a four week period, May 1-28, 1961, inclusive. Information was collected on the age, sex, and race of the patient; date and amount administered; procedure, and percentage thyroid uptake (if done). At a later date the clinics were asked to supply us with information on the total specific activity of I-131 that they had on hand at the initiation of the study, and on the amount that was shipped to them from May 1-28. Unfortunately, no information was requested on the amount remaining of May 29.

A single form was completed for each patient. If a patient received two separate tracer doses, he was counted twice. The twenty-four clinics completed 2100 questionnaires in the four week period. Ninety-seven of the forms were discarded for various reasons. One hospital participated for only two weeks while the totals of three peripheral hospitals were included with those from one major center. Information from two private offices was included in the data as they represented an extension of actual hospital practice.

PROCEDURES

Of the administrations 1,179 (59%) were for uptake studies, 530 (26.4%) for uptake and scanning procedures, and 70 (3.5%) for scanning and localization tests (Table II). Thirty-two various other individual procedures or combinations thereof accounted for the remaining 224 (11.2%) administrations. Of these, combinations of uptakes with other tests (81 instances), combinations of uptake

TABLE I

GEOGRAPHIC LOCATION OF HOSPITALS

City	*Number*
New York City	5
Boston	3
Los Angeles	2
Cleveland	2
Baltimore	2
Rochester, New York	2
Rochester, Minnesota	1
Nashville	1
New Orleans	1
Cincinnati	1
Chicago	1
Madison	1
St. Louis	1
San Francisco	1
	24

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FORM APPROVED
BUDGET BUREAU NO. 68-R745

DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
WASHINGTON 25, D. C.

SURVEY OF DIAGNOSTIC USE OF I-131
FOR
EVALUATION OF THYROID GLAND

CENTER NO. _____

HOSPITAL NO. _____

AGE	SEX		RACE	
_____ YRS. *(At last bthdy)*	MALE	☐1	WHITE	☐1
	FEMALE	☐2	NON-WHITE	☐2

DATE OF ADMINISTRATION: _____
(month – day)

AMOUNT ADMINISTERED : _____
(in microcuries)

PROCEDURE:

UPTAKE ONLY ..... ☐1

SCANNING OR LOCALIZATION ONLY ..... ☐2

UPTAKE AND SCANNING ..... ☐3

OTHER ..... ☐4

IF OTHER, SPECIFY _____

_____

UPTAKE:

AT 6 HOURS : _____ % OR

AT 24 HOURS : _____ % OR

AT _____ HOURS: _____ %
(specify)

_____

Figure 1

TABLE II

	Number	*Percent*
Total Completed Forms (May 1-28)	2100	
Forms Discarded	97	
Total Administrations	2003	100
Uptakes	1179	58.9
Uptakes and Scan	530	26.4
Scan or Localization	70	3.5
Other Procedures:	224	11.2
Uptake and Other	81	
Uptake and Scan and Other	63	
24 Hour Conversion Ratio	28	
Miscellaneous	52	

plus scans with other tests (63), and 24 hour conversion ratios (28) constituted the majority.

DAYS OF ADMINISTRATION

I-131 was administered only 3 times on the 4 Saturdays in the study and only 27 times on the Sundays. The remaining number of administrations were approximately equal on Mondays through Thursdays, while they decreased to about half on Fridays.

The number of administrations by week did not vary greatly. The second and third weeks of the study were approximately equal while the first and the fourth weeks, although less than the second and third by about 50 cases each, were also approximately the same.

TABLE III

UTILIZATION OF I-131 BY ACTIVITY

	(*mc*)
Amount available on April 30, 1961	941
Amount received May 1-May 28, 1961	5433
Amount used for uptakes, uptakes and scans, or scans alone	94
Amount used for other diagnostic tests	26
Amount remaining on May 29 *unknown*, but assumed to be	941
Percent I-131 used diagnostically	2.2%

$$\left(\frac{120}{5433} \times 100\right)$$

AMOUNT OF I-131 AVAILABLE AND THE AMOUNT USED

On hand at the clinics were 941 millicuries of I-131 on April 30, and 5433 millicuries were received from May 1-28 (Table III). No information was available on the amount of I-131 remaining on May 29. One of the large centers unfortunately did not furnish us with this information, and of those that did, they did so only for their clinics and not necessarily for the entire hospital. Ninety-four millicuries were used for uptakes, uptakes and scans, or scans only. An additional 26 millicuries were used for other thyroid diagnostic procedures. The fate of the remaining I-131 is unknown, but it is to be presumed that it was used therapeutically, for non-thyroid tests, or for research. The remaining amount undoubtedly decayed, was discarded, or was used in the following month.

Because of the lack of information mentioned above, it is difficult to make an accurate estimate of the percentage of I-131 used diagnostically. However, if we assume that the amount remaining at the end of May was about the same as the amount left at the end of April, then only approximately 2.2% $\left(\frac{94 + 26}{5433} \times 100\right)$ of the total amount of I-131 available to these clinics in the four week period was used for diagnostic thyroid tests. This agrees with previous conclusions that information on the total amount of an isotope shipped from a factory cannot be used as an index of its consumption. (4)

A variety of doses were used for the different procedures with the range extending from one to 10,000 microcuries. The median doses for uptakes, uptake and scans, and scans alone were 8.97, 44.5, and 33.9 microcuries, respectively.

AGE AND SEX OF PATIENTS

The patients ranged in age from under one to 94 years. Only 32 of them were less than 15 years of age, while only 272 were less than 30. The median age for females was 49.4, while the median age for males was 52.1. The overall median age was 50 years (Table IV).

Of the patients 1586 were females while 492 were males. The sex was unknown in 22 cases.

TABLE IV

AGE AND SEX OF PATIENTS

Minimum	< 1 year
Maximum	94 years
Under 15 years	32 patients
Under 30 years	272 patients
Median age:	
males	52.1
females	49.4
overall	50
Number of females	1586
Number of males	492
Number of undetermined sex	22

DISCUSSION

Although these figures are limited in scope, they are the only ones of this type available, and they do reveal several worthwhile points. First, it is feasible for an individual dispensing isotopes to complete a simple form containing pertinent information about the patient and the isotope. It is also feasible for an agency to collect and analyze it. This information might be very valuable for population dose assessment and for epidemiological investigations.

Uptake measurements were the most frequent study (59%) with a median dose of 8.97 microcuries administered. A combination of uptake and scans was second (26%) with a median dose of 44.5 microcuries, while scans alone were performed rarely (median dose 33.9 microcuries). A variety of combinations and other individual procedures accounted for approximately 11 per cent of the total number of administrations.

The relatively few numbers of administrations and the small percentage by activity of I-131 used diagnostically were surprising. These were 24 major clinics and yet an average of less than 100 patients per month at each received tracer doses of I-131. The minimum number at any one clinic was 25, while the maximum number was 250. Furthermore, only about 2 per cent of the I-131 shipped to the clinic or on hand at the time the study began, was used for thyroid diagnostic tests during the period of May 1-28.

Only 32 children received isotopes. All of the hospitals except one have pediatric wards; several of the clinics do all the isotope work for adjoining pediatric hospitals. Most of the departments are reluctant to administer isotopes to children while only one flatly refuses. The range of doses was from 2 to 60 microcuries. The problem of children receiving isotopes, at least for diagnostic purposes, therefore, seems less than previously assumed.

SUMMARY

Twenty-four major hospital centers dispensed 2100 tracer doses of I-131 for purposes of evaluation of the thyroid gland from May 1-28, 1961. The most frequent procedure was an uptake study. The average patient was a 50 year old female; only 32 children were included. The doses administered are described, and it is seen that they represented a small fraction of the total I-131 available to the hospital.

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The Relative Mean Transit Times of Red Cells and Plasma in the Portal Circulation of the Dog[1,2]

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Los Angeles

INTRODUCTION

It has been known for a number of years that the total body hematocrit is lower than the large vessel hematocrit. This had been shown by indirect means (1) and has been demonstrated by the simultaneous measurement of the plasma volume and red cell mass by several investigators (2). The ratio of the total body hematocrit to large vessel hematocrit (hereafter called hematocrit ratio in this paper) in man under normal conditions is about 0.91. The hematocrit ratio may be considerably lower than normal in such conditions as acute burns (3), shock (4), and, to a lesser degree, in congestive heart failure (5). We have found the hematocrit ratio to be as low as 0.68 in some patients with pheochromocytoma (6).

It would be proper to conclude that blood in portions of the vascular bed is present at a lower hematocrit than that in the veins and arteries from which blood samples are usually obtained. The notable exception arises in the case of the spleen where the organ hematocrit is higher than in the peripheral blood. Funderberg *et al.* (7) noted that patients with massive splenomegaly had an average hematocrit ratio of 1.156.

The recognition of this phenomenon is important because of its effect on the calculation of the whole blood volume from either a red cell mass or plasma volume.

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[2]This research was supported in part by research grant Nos. H-2195 and H-4745 from the National Heart Institutes of Health, United States Public Health Service, and by the Los Angeles County Heart Association.

In 1929, Fahraeus (8) observed that in glass tubes from 0.05 to 0.1 mm in diameter, red cells flow in the central stream and at a faster rate than plasma. A few studies of comparative flow-dilution curves of red cells and plasma have been made in the pulmonary (2, 9, 10, 11, 12) and peripheral (13, 14, 15) circulation. Although in most of these, no values were given for mean transit times, all agree that red cells traverse the vascular bed faster than plasma.

We have previously reported (16) the mean transit times, whole blood flow, volumes of distribution, and hematocrit ratios of simultaneously injected labelled red cells and labelled plasma in the pulmonary, leg, and head circulation of the dog. This is a report of the relative velocities of red cells and plasma in the portal (hepatic) circulation of the dog.

METHOD AND APPARATUS

The instrumentation has been previously described (16). Figure 1 is the block diagram of the apparatus. Dogs weighing 11.4 to 22.9 kg were sedated with nembutal. To test the portal circulation, a polyethylene catheter was passed via the right jugular vein into the hepatic vein to obtain the outflow sample, and another short catheter was introduced into the portal vein via the ligated splenic vein for the injection of the tracer.

Preparation of test material: A sample of the dog's red cells was tagged with high specific activity Cr^{51}, and then sufficient RISA®[1] was added to give approximately equal counting rates on the respective recording channels. This injection mixture contained about 75 microcuries of Cr^{51} and 8 microcuries of I^{131} as RISA

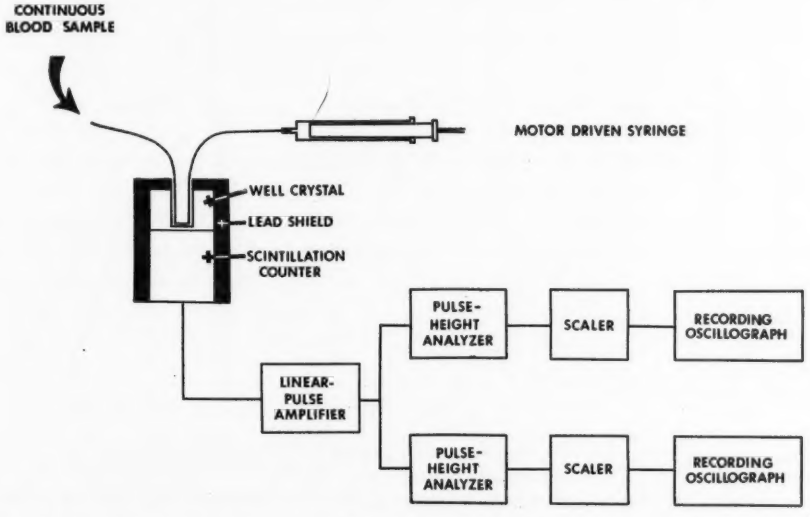

Fig. 1. Arrangement of equipment for the study. Continuous sample obtained from hepatic vein.

[1]Abbott Laboratories, North Chicago, Illinois.

per ml with a hematocrit of about 75 per cent. A standard dilution (1:100) was made of the injection mixture.

Method of test: In a typical test the sampling pump and the recorder were allowed to run for 10 seconds or more to obtain the total background counting rate.[1] The mixed tracer material was injected into the appropriate catheter and the time of injection recorded on the tracing. To measure portal circulation either 1 or 2 ml of the mixture with 5 ml saline rinse was injected into the portal vein. (RISA could be prevented from adhering to the plastic tubing by a previous flushing with carrier albumin or blood). Sampling and recording were continued until recirculation could be recognized. A portion of sampled blood obtained near the circulation peak was reserved for duplicate hematocrits. All hematocrit determinations were made the same way, and were corrected for the amount of plasma (3%) in the red cell zone.

The cross-channel contribution of each isotope was determined just before and after each run. Periodically the standard solution was introduced into the tubing in the well crystal and counted.

To check the system for the effect of laminar flow in the sampling tubing a three-way stopcock arrangement was set up so that sampling could be suddenly changed from a beaker of water to a beaker of isotope solution without introducing air into the system. The sampling rate was held constant at 1 ml/sec

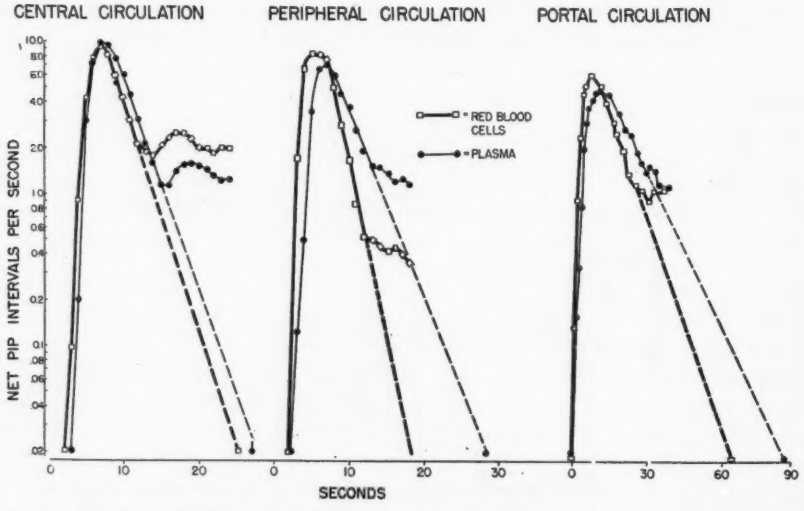

Fig. 2. Typical graphs of the simultaneous measurement of labelled red cells and labelled plasma in the pulmonary, head, and portal circulation of the dog. Net counts per sec. can be obtained by multiplying net pip intervals per sec. by the scale setting (64).

[1]Total background includes instrumentation background and blood background from any previous injection.

and the counting geometry at about 0.2 ml, as in the animal studies. It required 1.3 seconds for the counting rate to change from two to 90 per cent of the counting rate of the isotope solution.

It is not advisable to have more than about six determination in the same dog, because of the rising background.

Calculation of data: The time of injection was corrected for traverse time of blood sample from catheter tip to well crystal. From this point of reference net "pip intervals"[1] per second were found by subtracting background from the number of pip intervals actually counted at each second (17).

At a scale of 64 counts per pip, the peak values ranged from 8 to 15 pip intervals per second. As background increased with successive runs, the scale was raised to 128 counts per pip. (With a recording paper speed of 50 mm per second, up to 40 pips per second were readily identifiable.)

Correction was then made for cross channel activity, and the resulting values were plotted on semilogarithmic paper to obtain the extrapolated portion of the downslope. Mean transit times (MTT), whole blood flow, and volumes were calculated from these using the following formulas.

$$\text{Whole Blood Flow (ml/sec)} = \frac{C_s \times I \times \text{dilution of standard}}{C_{av} \times T}$$

C_s is the counting rate of the respective standard, I equals the volume injected, C_{av} equals the average concentration, and T is the time base of the curve.

$$MTT = \frac{\sum (C \times T)}{\sum C}$$

Where C is concentration and T is elapsed time of each concentration from zero time (corrected injection time).

The mean transit times of the whole blood flow values were calculated from both the red cell and plasma curves. The red cell flow values was calculated from the whole blood flow of the red cell curve and from the hematocrit. Plasma flow value was obtained similarly using the plasmacrit and whole flow of the RISA curve. The distribution volume of red cells and plasma was calculated from the product of the respective mean transit times and flow values. The calculated hematocrit of the circulating portal blood was then obtained from the plasma and red cell distribution volumes. The hematocrit ratio was then obtained by dividing the circulating hematocrit by the large vessel hematocrit at the time of the test.

The statistical analysis of the method has been reported elsewhere (16).

In some animals the exponential portion of the downslope of the curve was deemed inadequate for statistical reasons. Accordingly we omitted the data from those animals in which the portion for extrapolation demonstrated less than a 50 per cent decrease in concentration before obvious recirculation.

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[1]Pip interval is the distance between consecutive pips on the recording. Counts could be determined by multiplying the number of pip intervals by the scale setting.

RESULTS

Figure 2 shows dilution curves of actual tests of the pulmonary, head, and hepatic circulation showing the counting rates of Cr^{51} labelled red cells and RISA labelled plasma as a function of time. The curves selected for this figure were those with mean transit time values near the average for the group.

There is a slight but definite delay in the formation of the plasma curve as compared with the red cell curve in the central circulation. The difference between the MTT of red cells and plasma is even more noticeable in the head and portal circulation curves.

Portal Circulation: Table I presents the results of the hepatic portal tests in 8 dogs. The average mean transit time (MTT) for plasma was 19.89 ± 8.09 sec. The average MTT for red cells was 13.20 ± 5.54 sec. The average MTT for red cells was shorter in all instances and averaged 6.69 ± 3.52 sec. less than the MTT for plasma. The per cent difference between the two mean transit times ranged from 8.5 to 51.7 and averaged 32.5 ± 12.5.

The average total whole blood flow through the portion of the liver tested was 42.0 ml/min/10 kg. The whole blood flow values computed from Cr^{51} labelled red cells did not differ significantly from those computed from the corresponding RISA data. The capillary hematocrits calculated from the distribution volumes were 53 to 90 per cent (average 73 ± 10 per cent) of the large vessel hematocrit.

Table II compares the average results of the plasma and red cell flow rate studies of four capillary beds.

TABLE II

AVERAGE RESULTS OF DIFFERENTIAL FLOW RATES IN THE DOG

	Central (Pulmonary) Circulation	*Peripheral (Head) Circulation*	*Peripheral (Leg) Circulation*	*Hepatic (Portal) Circulation*
Number of Dogs	20	6	20	8
Number of Determinations	20	10	27	16
Plasma MTT (sec)	8.77 ± 1.65	16.50 ± 7.00	15.51 ± 9.61	19.89 ± 8.09
Red cell MTT (sec)	8.44 ± 1.38	14.30 ± 5.94	13.91 ± 8.76	13.20 ± 5.54
Difference (sec)	0.33 ± 0.23	2.20 ± 1.30	1.61 ± 1.35	6.69 ± 3.52
Per Cent Difference	3.7 ± 2.2	12.8 ± 5.5	10.7 ± 5.9	32.5 ± 12.5
Hematocrit Ratio*	0.97 ± 0.04	0.90 ± 0.02	0.89 ± 0.07	0.73 ± 0.06

$$\text{*Hematocrit Ratio} = \frac{\text{Calculated PCV from red cell and plasma volume of test}}{\text{Large vessel PCV at time of test}}$$

TABLE I

NORMAL VALUES OF THE PORTAL CIRCULATION

Dog No.	*Mean Transit Time (sec)*				*Mean Arterial Pressure (mm Hg)*	*Flow Rate (ml/min/ 10 kg)*	*Peripheral Volume by MTT (ml)*			*Large Vessel Hematocrit Percent*
	Plasma	*RBC*	*Diff.*	*Percent Diff.*			*Plasma*	*RBC*	*PCV Ratio*	
1	16.99	13.69	3.30	19.4	140	81.5	269	96	0.72	36.5
1	8.37	6.96	1.41	16.8	132	68.4	118	35	0.64	36.0
2	11.67	10.68	0.99	8.5	78	96.0	119	80	0.90	44.4
3	20.40	13.86	6.54	32.1	91	39.3	125	88	0.77	53.3
4	21.14	15.43	5.71	27.0	113	19.3	70	41	0.87	42.7
4	21.10	17.66	3.44	16.3	68	29.8	117	65	0.81	43.9
5	15.70	7.85	7.85	50.0	106	55.0	201	46	0.59	31.6
5	16.28	7.86	8.42	51.7	103	67.4	196	48	0.64	31.5
5	20.79	11.93	8.86	42.6	97	45.6	209	65	0.74	32.0
6	20.28	11.79	8.49	41.9	151	17.7	84	31	0.89	40.2
6	21.55	12.43	9.12	42.3	146	18.2	73	25	0.68	41.1
6	22.82	13.44	9.38	41.1	158	14.5	72	32	0.74	41.6
6	20.61	14.94	5.67	27.5	148	41.0	231	66	0.53	41.8
7	46.25	30.93	15.32	33.1	94	25.0	258	122	0.72	45.2
8	14.12	10.55	3.57	25.3	132	30.2	74	42	0.81	44.1
8	20.20	11.22	8.98	44.5	130	23.5	82	35	0.69	43.3
Mean	19.89	13.20	6.69	32.5	117.9	42.0	143.6	57.3	0.73	40.6
S.D.	±8.09	±5.54	±3.52	±12.5					±0.10	±5.6

In each of the capillary beds the MTT for plasma was significantly longer ($p < 0.01$) than for red cells. In each capillary bed the circulating hematocrit was significantly lower ($p < 0.01$) than the large vessel hematocrit obtained at the time of the test.

The per cent lag in plasma flow behind red cell flow is greatest in the hepatic circulation and least in the pulmonary circulation. The results of the head circulation did not differ significantly from those of the leg.

The PCV ratio of the head and leg circulation was significantly less ($p < 0.01$) than that of the central circulation. The PCV ratio of the hepatic circulation was significantly less ($p < 0.01$) than that of the head and leg circulation.

DISCUSSION

The normal ratio of total body hematocrit to large vessel hematocrit has been reported as 0.91-0.94. Assays of tissues and organs for red cell and plasma content (18, 19, 20, 21) have established that the tissue hematocrits are significantly lower than the large vessel hematocrit except in the spleen, where the reverse is true.

This difference in the hematocrit ratios can be adequately explained on the basis of the observed differences of flow rates of red cells and plasma. Reported studies of the central circulation (2, 9, 10, 11, 12), in which the various methods for tracing plasma and red cells were used, have consistently shown that red cells flow slightly faster than plasma. The high hematocrit ratio of the lung obtained by these circulation studies would indicate that the lung vascular bed does not play a significant role in lowering the total body hematocrit.

Although various workers (13, 14, 15) have shown that concentration curves of red cells form sooner than those of plasma in the peripheral circulation, the capillary hematocrits have not differed significantly from the large vessel hematocrits in the reported studies. Using the Bradley equilibruim technique Sliwinski and Lilienfield (22) found the hematocrit of the small vessels of the dog leg to be significantly lower than that of the large vessels.

Our own results show the circulating hematocrits of the lung, head, leg and portal vascular beds to be significantly lower than the large vessel hematocrit. In the formula for calculating circulating hematocrit used by Lilienfield (14) the whole blood flow (ml/sec) was considered to be the same whether estimated by the red cell or plasma tracers. Since the whole blood flow measured by the red cell tracers is not necessarily equal to the whole blood flow measured by the plasma tracer, we have used the whole blood flow value and MTT of each curve for the calculation of the volume of dilution of the tracers. If we ignore the whole blood flow and use Lilienfield's formula in the calculation of capillary hematocrit, our data gives an average hematocrit ratio of 0.77 ± 0.11. This values does not differ significantly ($p > 0.3$) from the 0.73 ± 0.06 obtained using the whole blood flow of the curves.

Our values for the whole blood flow of the hepatic portal circulation are lower than those reported by the bromsulfalein method (23) and the electro-

magnetic flowmeter (24). We did not attempt to measure the total flow of the portal system. Furthermore, the splenic vein was ligated in our procedure.

From the work of Fahraeus (8) on blood flow through glass tubes we would expect little or no difference in the mean transit times of red cells and plasma except in those vessels in which the diameter of the vessel is less than a critical diameter of about 0.25 mm.

If it were possible to test only that portion of the vascular bed with vessels smaller than the critical diameter, the difference between the mean transit time of red cells and plasma should be even greater than we found it. Since in actual practice the blood from the point of injection to the site of sampling is contained in vessels of widely varing diameter, there is a consequent averaging of the difference in the relative velocity of red cells and plasma and in the circulating hematocrit.

Poisseuille's equation for the flow of newtonian fluids, applied to blood flow in cylindrical tubes, has been used to describe the flow of blood in the vessels of the body. However, Fahraeus (8) felt that blood *in vivo* does not follow this law. Arteries and veins are not cylinders but truncated cones with only the capillaries being cylinders. Further, the vessels walls have a parameter of elasticity. Plasma is a non-newtonian fluid with viscosity changing with velocity of flow (25). An equation to describe the pulsatile flow of non-newtonian fluid containing solid particles in a group of paralled-connected elastic tubes which are first reducing cones, cylindrical tubes, and then enlarging cones would be quite complex.

Bernoulli's law states that the lateral pressure of a fluid in a tube is inversely proportional to the velocity of flow. A red or white cell flowing between the stream center and vessel wall would be exposed to a lower pressure on the side facing the axial stream than on the wall side. This would draw the cellular structures into the axial portion of the stream. The smaller the blood vessels, the greater would be the velocity gradient between the axial and lateral portion. As a result the cellular structures in a smaller vessel would be forced relatively further into the axial portion of the stream. Vejlens, (26) suggested from mathematical calculations years ago that the particles would not be driven to the center of the stream but only part way then straight ahead.

The application of Bernoulli's and Posseuille's laws explains the greater average velocity of red cells as compared with plasma, but these laws fall short of quantitatively expressing the flow of blood in the arterioles, capillaries, and venules. We would not expect these physical laws to apply to extremely small capillaries. Some of the peripheral capillaries are so small that red cells must be molded or must distend the capillary in order to traverse them. In such small vessels the plasma may travel faster than the cells.

SUMMARY

The relative flow rates of red cells and plasma were measured in the hepatic portal circulation of the dog by injecting a mixture of Cr^{51}-labelled red cells and I^{131}-labelled plasma into the freely flowing portal vein circulation. The mean

transit (MTT), whole blood flow, and volume of dilution of each phase in the hepatic venous blood were calculated from the isotope dilution curves obtained from the simultaneous counting of Cr^{51} and I^{131} with differential pulse height analyzers.

In sixteen tests of the hepatic portal circulation the average MTT for plasma and red cells was 19.89 ± 8.09 and 13.20 ± 5.54 seconds respectively. The average ratio of the hepatic circulating hematocrit to the large vessel hematocrit was 0.73 ± 0.06.

Comparative values for other vascular beds are given for the pulmonary (central) circulation, the head, and leg vascular beds of the dog.

In every hepatic portal circulation determination the MTT of plasma measured greater than that of red cells, and the average per cent difference between the two was significantly greater ($P < 0.01$) than the corresponding value for the pulmonary, leg, and head vascular beds.

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Announcement to Authors
Preliminary Notes

Space will be reserved in each issue of THE JOURNAL OF NUCLEAR MEDICINE for the publication of one preliminary note concerning new original work that is an important contribution in Nuclear Medicine.

Selection of the preliminary note shall be on a competitive basis for each issue. One will be selected after careful screening and review by the Editors. Those not selected will be returned immediately to the authors without criticism. Authors may resubmit a rejected or revised preliminary note for consideration for publication in a later issue. The subject material of all rejected manuscripts will be considered confidential.

The text of the manuscript should not exceed 1200 words. Either two illustrations, two tables, or one illustration and one table will be permitted. An additional 400 words of text may be substituted if no tables or illustrations are required. Only the minimum number of references should be cited.

Manuscripts should be mailed to the Editor, Dr. George E. Thoma, St. Louis University Hospital, 1325 South Grand Blvd., St. Louis 4, Missouri. They must be received before the first day of the month preceding the publication month of the next issue, e.g., preliminary notes to be considered for the September, 1963 issue must be in the hands of the Editor before August 1, 1963.

JOURNAL OF NUCLEAR MEDICINE 4:306-311, 1963

Computers in Activation Analysis

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INTRODUCTION

The Radioisotope Service of the Veterans Administration Hospital, Omaha, Nebraska, uses a General Atomic Triga Reactor in medical research. One of the research projects is to develop a neutron activation analysis system that will aid in nuclear medical research. One application under development at present is the analysis of blood serum by activation analysis.

The present system includes the Triga Reactor, a RIDL 400 channel analyzer and an IBM 1620 computer. The programming language used is 1620 Fortran•Fortan (FORmula TRANslation) is an automatic coding system that allows the scientist to program with only a slight knowledge of the computer. There are over twenty small, medium, and large scale computers that have FORTRAN processors. This paper presents a computer method of solution used in neutron activation analysis using IBM 1620 FORTRAN programs.

THE PROBLEM

The basic assumption in our neutron activation analysis system is that the spectra of irradiated elements in a composite sample add linearly when counted by a multichannel analyzer. If this assumption is true, the proportionate parts of a composite spectrum may be assigned to the proper elements by solving a set of simultaneous linear equations of order K of the number of radioactive elements in the composite.

As an example of such a method of solution, a three element composite will be used whose individual element spectra and composite spectrum are shown in Figure 1.

The three equations for the total counts in the most energetic photopeak of elements 1, 2, and 3 are:

$$a_{11} X_1 + a_{12} X_2 + a_{13} X_3 = b_1$$
$$a_{21} X_1 + a_{22} X_2 + a_{23} X_3 = b_2$$
$$a_{31} X_1 + a_{32} X_2 + a_{33} X_3 = b_3$$

where the b_1, b_2, and b_3 are five channel sums of the counts of the most energetic photopeaks of elements 1, 2, and 3. For example, the total counts of the composite spectrum in the channels of the most energetic photopeak of the third element are the sum of the counts due to elements 1, 2, and 3 of the composite. The coefficients a_{kl} of the variables X_k are the ratios defined by $a_{kl} = \frac{N_{lk}}{N_{ll}}$ where N_{lk} is the number of counts of the i(th) element at the most energetic photopeak of element K. N_{ll} is the number of counts of the i(th) element in its own most energetic photopeak. The values of a_{kl} are determined from the standard spectra of the elements in the composite. A standard spectrum for an element is found by processing individual activation runs of given mass for each element using a standard set of handling procedures. These spectra are processed through a statistical computer program to get a mean curve that has a standard deviation of less than five per cent. Figure 2 shows the a_{kl} for element 3.

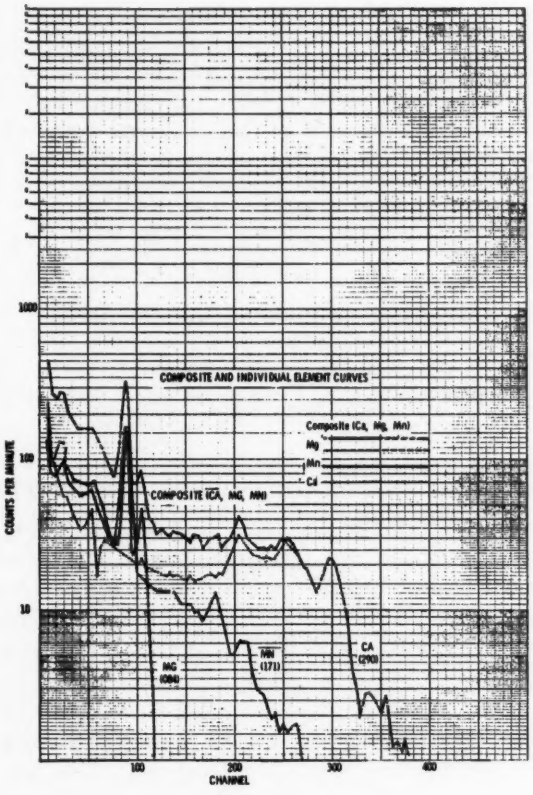

Figure 1

a_{11} is the ratio of the counts of elements 1 in its own most energetic photopeak to itself. $a_{11} = 1$. a_{21} is the ratio of the counts of element 1 in the most energetic photopeak of element 2 to those of element 1 in its most energetic photopeak.

$$a_{21} = \frac{N_{12}}{N_{11}} \qquad \text{and} \qquad a_{31} = \frac{N_{13}}{N_{11}}$$

The ratios from the spectra of elements 1 and 2 are found in the same manner to get all the a_{ki} for the three element composite.

The solution of the three equations for X_1, X_2, and X_3 finds the counts of each element in its most energetic photopeak that are due to that element only, which is what we want—the separation of the composite into its component parts. Element masses are then computed by $\text{MASS} = N_{kk} \frac{\text{STD MASS}}{\text{COUNTS}}$.

THE METHOD OF SOLUTION

A matrix method is used to solve the simultaneous linear equations as follows: Let A represent the matrix of coefficients.

$$A = \begin{bmatrix} a_{11} & a_{12} & a_{13} \\ a_{21} & a_{22} & a_{23} \\ a_{31} & a_{32} & a_{33} \end{bmatrix}$$

$$\text{Let } X = \begin{bmatrix} X_1 \\ X_2 \\ X_3 \end{bmatrix} \text{ and } B = \begin{bmatrix} b_1 \\ b_2 \\ b_3 \end{bmatrix}$$

$$\text{Then } AX = \begin{bmatrix} a_{11} & a_{12} & a_{13} \\ a_{21} & a_{22} & a_{23} \\ a_{31} & a_{32} & a_{33} \end{bmatrix} \begin{bmatrix} X_1 \\ X_2 \\ X_3 \end{bmatrix} = \begin{bmatrix} a_{11}X_1 & a_{12}X_2 & a_{13}X_3 \\ a_{21}X_1 & a_{22}X_2 & a_{23}X_3 \\ a_{31}X_1 & a_{32}X_2 & a_{33}X_3 \end{bmatrix} = \begin{bmatrix} b_1 \\ b_2 \\ b_3 \end{bmatrix} = B$$

The system of linear equations can be represented in matrix form by $AX = B$. Multiply by A^{-1} (the inverse of A):

$$\begin{aligned} A^{-1}\ (AX) &= A^{-1}B \\ (A^{-1})\ (A)X &= A^{-1}B \\ I_3X &= A^{-1}B \\ X &= A^{-1}B \end{aligned}$$

Or, the values of X_1, X_2, X_3 that are $X = \begin{bmatrix} X_1 \\ X_2 \\ X_3 \end{bmatrix}$ may be found by inverting the matrix A and by multiplying by $B = \begin{bmatrix} b_1 \\ b_2 \\ b_3 \end{bmatrix}$.

COMPUTER PROGRAMS

(a) PHASE #1 is an IBM 1620 Fortran statistical routine for creating a standard element tape. The program accepts a variable number of individual data tapes. It then computes the mean, standard deviation, and per cent error for each of the 400 channels. The output is a printout of the statistics for all 400 channels and a punched paper tape that is the mean standard tape for that element. A correction for flux variation is incorporated in the program.

(b) MATRIX COEFFICIENT AND MASS RATIO GENERATOR

This IBM 1620 Fortran program computes the matrix coefficients a_{kl} from the N_{ij} counts from the standard element spectra. Since the standard elements will have different half lives and may have different live times, elapsed times, cooling times, and masses, all the a_{kl} of the standards are converted to the cooling time of the known composite by using the formula $A_t = A_o e^{-\lambda t_1}$ and mass ratios for each element are computed. Live time is the actual time the electronic circuitry of the multichannel analyzer is accepting pulses. Elapsed time is actual clock time for the analyzer to count for a given live time. Cooling time is the interval between the time of removal of the sample from the reactor and the mid-point of elapsed time.

A decay time correction to activity is also made to account for multichannel analyzer response to non-linear disintegration rate as shown in Figure 3. (2)

$$\text{For example, if } \frac{\Delta t}{\text{half-life}} - 10.0, \frac{a_c}{a} = 0.218.$$

$$\text{If } \frac{\Delta t}{\text{half-life}} = 1.0, \frac{a_c}{a} = 0.980.$$

The output on paper tape is the a_{kl} and mass ratios needed in the eleven element analysis program.

(c) ELEVEN ELEMENT ANALYSIS PROGRAM

This IBM 1620 Fortran program has as input the a_{kl} and mass ratios of program above plus the counts of the composite in the most energetic photopeaks of the elements in the composite spectrum and the composite live time. The printed output is the original matrix, the counts in each element's most energetic photopeak due to that element (the $X = \begin{bmatrix} X_1 \\ X_2 \\ X_3 \end{bmatrix}$ of the simultaneous linear equations), the mass in mg/given amount in cc's of each element, the inverted matrix, and the reinverted matrix. The reinverted matrix is compared to the original matrix to check for stability.

AN EXAMPLE

Table I is the printout of the solution of a three-element composite where

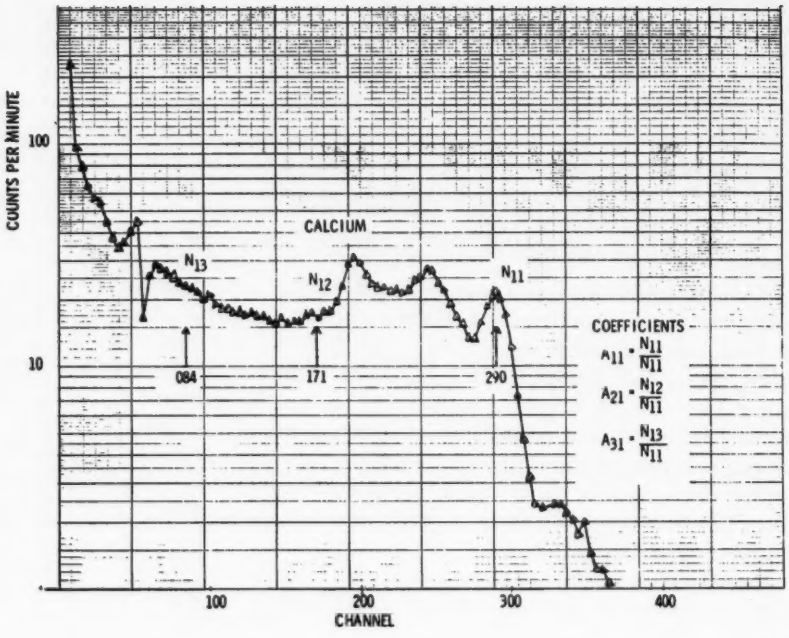

Figure 2.

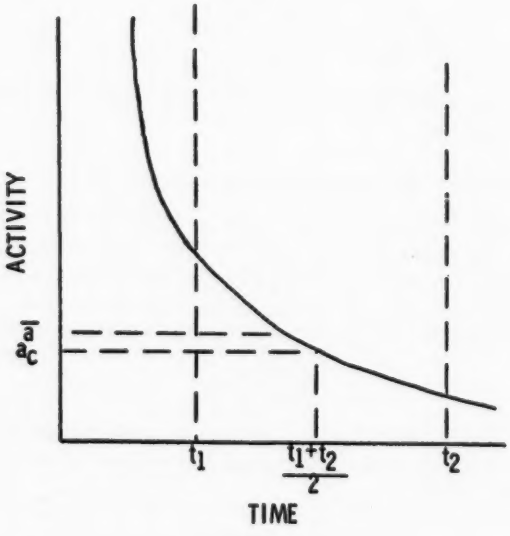

Figure 3.

the elements are calcium, manganese, and magnesium. The composite is of the amount of each standard element. The differences between the chemical analysis and the matrix solution are shown in the table below.

	CHEMICAL ANALYSIS		*MATRIX ANALYSIS*		
	Cts./Min.	*Mass (Mg/3 cc)*	*Cts./ Min.*	*Mass (Mg/3 cc)*	*MATRIX CHEM.*
Ca	103.4	0.33	101.64	0.321	98.3%
Mn	61.9	$9.108X10^{-5}$	64.33	$9.476X10^{-5}$	103.9%
Mg	757.4	0.09	729.97	$8.562X10^{-2}$	96.4%

CONCLUSION

Such a method of solution is basically as good as the purity of the standard chemicals and the accuracy of the reactor and multichannel analyzer instrumentation and handling procedures. These limitations apply to a matrix solution of simultaneous linear equations in two ways. One, the order of magnitude of the ratio of the least active to the most active element must not exceed 10^3 for the solution of the amount of the least active element to be accurate enough to be usable. Two, all elements in a given composite must be known and must be available in a library of standards.

TABLE I

MATRIX SOLUTION OF 3X3 COMPOSITE 6/15/62

LOAD DATA

1.0000000	1.6850766E–02	7.8755878E–04	Original Matrix
.80361597	1.0000000	3.6854930E–03	
1.0547533	10.841522	1.0000000	
101.64112	.32091769		Counts and Mass for Each Element
64.329282	9.4756743E–05		
729.96620	8.5620261E–02		
1.0078157	−8.7260590E–03	−7.6155412E–04	Inverse Matrix
− 83952332	1.0488880	−3 2044956E–03	
8 0387134	−11.362338	1 0355447	
.99999994	1.6850766E–02	7.8755870E–04	Reinverted Matrix
.80361602	1.0000001	3.6854933E–03	
1.0547531	10.841523	1.0000001	

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Influence of Plasma from a Variety of Stressed Animals on I^{131} Uptake in Chick Embryos[1,2]

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INTRODUCTION

Plasma from the rat, guinea pig, and rabbit in addition to plasma from the chicken (1) exposed to whole-body x-irradiation when injected into 15 day old chick embryos significantly increases the uptake of I^{131} in the thyroid. To determine whether or not this phenomenon is dependent upon the intact endocrine system, and whether or not other forms of stress can also elicit the phenomenon, studies have been made of the effect of plasma from x-irradiated, adrenalectomized, thyroidectomized and hypophysectomized rats and from rats subjected to cold, heat, starvation and exhausting exercise on the I^{131} uptake by the thyroid of 15-16 day old chick embryos.

MATERIALS AND METHODS

Fifteen day old fertilized eggs of a White Leghorn Cross were injected with 2.5 μc of I^{131} in 0.1 ml of isotonic saline and 0.1 ml of pooled plasma, where indicated, via the air sac. Approximately 24 hours later the necks containing the thyroids were excised and counted in a scintillation type well counter. The counting error was 1 per cent or less. Factors for the whole-body x-irradiation were 300 KV, 20 MA, 3.5 mm Cu filter. At a 70 cm TSD the output was 23.5 r/min. The animals were all adult males. The Wistar rats weighed 200 gm; the guinea pigs 400-500 gm; and the albino rabbits weighed 6-7 lbs. The diet was Purina lab

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TABLE I

SCHEME OF THE EXPERIMENTS

Experiment	*Animal*	*Gland Extirpated*	*Stress*	*Duration of Stress*	*Dose of X-Ray*	*Post Stress Time of Bleeding*
1.	Rat	None	X-Ray	Acute[1]	200–600 R	48 Hr.
2.	Guinea Pig	None	X-Ray	Acute	600 R	24-72 Hr.
3.	Rabbit	None	X-Ray	Acute	600 R	2-48 Hr.
4.	Rat	Hypophysis	X-Ray	Acute	400–600 R	48 Hr.
5.	Rat	Thyroid	X-Ray	Acute	500–600 R	48 Hr.
6.	Rat	Adrenal	X-Ray	Acute	200–600 R	48 Hr.
7.	Rat	None	Swimming Daily to Exhaustion	4-7 days	None	
8.	Rat	None	Exposure to 5°C	7 & 25 days	None	
9.	Rat	None	Exposure to 35°C	1 & 2 days	None	
10.	Rat	None	Starvation	3 & 7 days	None	Last Day of Stress

1. Single Exposure.

chow and water ad libitum except that isotonic saline was given to the adrenalectomized and hypophysectomized rats. The exposures to heat and cold were made in a walk-in ventilated box. Forced swimming daily for 10-30 minutes constituted the exhausting exercise. All bleeding was via heart puncture with a heparin wetted syringe.

Data were analyzed for significance by means of the "t" test (2).

Table I outlines the experiments performed.

In Experiment 1 plasma obtained from rats 48 hours after whole body exposure to 200, 400 or 600 r of x-rays was injected into the eggs. The control plasmas for this and the following experiments were obtained from animals alike in all respects to the experimental animals except they were not stressed.

In Experiment 2 plasma obtained from guinea pigs 24, 48 or 72 hours after whole-body exposure to 600 r of x-rays was injected.

In Experiment 3 plasma bled from different rabbits at 2, 3, 18 and 48 hour intervals after whole-body exposure to 600 r was injected.

In Experiment 4 plasma from hypophysectomized rats obtained 48 hours after whole-body exposures to either 400 or 600 r of x-rays was injected.

In Experiment 5 plasma from thyroidectomized rats obtained 48 hours after whole-body exposures to either 500 or 600 r of x-rays was injected.

In Experiment 6 plasma from adrenalectomized rats obtained 48 hours after whole-body exposures to 200, 400 or 600 r of x-rays was injected.

In Experiment 7 plasma from rats swum to exhaustion once daily for 4 to 7 days was used.

In Experiment 8 plasma from rats kept at 5 C for periods varying from 7 to 25 days was injected.

In Experiment 9 the plasma injected was from rats exposed to 35 C temperatures for 1 to 2 days. Longer exposures caused death.

In Experiment 10 the plasma injected was from rats totally deprived of food for 3 to 7 days.

RESULTS

Tables II and III show the results obtained.

In Experiment 1 a significant increase in the thyroidal uptake of I^{131} was seen in those embryos injected with plasma obtained from rats 48 hours after their exposure to 200, 400 or 600 r of x-rays.

In Experiment 2 a significant increase in thyroidal uptake was seen in those embryos injected with plasma from guinea pigs obtained 48 hours after their exposure to 600 r. None was found for the 24 and 72 hour post-exposure plasmas.

In Experiment 3 the plasma from rabbits obtained 2 and 3 hours after their exposure to 600 r elicited a significant increase in the I^{131} uptake in the embryos' thyroids whereas the 18 hour plasma did not.

In Experiment 4 none of the plasmas from the hypophysectomized rats elicited a significant response.

In Experiment 5 plasma from thyroidectomized rats failed to elicit a significant increase in all but one instance.

TABLE II

EFFECT OF PLASMA FROM X-IRRADIATED ANIMALS ON UPTAKE OF I^{131} IN CHICK EMBRYOS

Experiment No.	*Stress*	*No. of Eggs*	*Counts/min. Mean Value*	*P*
1	Control Rat	39	93,569±6965[1]	
	200 R at 48 Hr.	40	115,652±7593	.025
	Control Rat	18	25,288±2785	
	400 R at 48 Hr.	30	34,346±2874	.025
	Control Rat	49	55,514±3852	
	600 R at 48 Hr.	50	79,274±4281	.0025
	Control Rat	41	34,534±2215	
	600R at 48 Hr.	33	42,142±1961	.0025
2	Control Guinea Pig	40	37,602±3234	
	600 R at 48 Hr.	40	45,518±2663	.05
	Control Guinea pig	40	72,008±5037	
	600 R at 24 Hr.	40	75,322±4228	> .05
	Control Guinea pig	40	29,266±2101	
	600 R at 72 Hr.	40	32,938±2210	> .05
3	Control Rabbit	40	60,695±2723	
	600 R at 2 Hr.	39	70,911±3943	.025
	Control Rabbit	26	63,331±5392	
	600 R at 3 Hr.	40	84,708±4681	.005
	Control Rabbit	37	62,282±3535	
	600 R at 18 Hr.	40	58,099±4051	> .05
4	Control Hypophyex rat	39	96,549±5722	
	400 R at 48 Hr.	40	104,458±4663	> .05
	Control Hypophyex rat	36	79,824±6027	
	600 R at 48 Hr.	40	71,348±5261	> .05
	Control Hypophyex rat	40	56,367±4126	
	600 R at 48 Hr.	40	60,031±4165	> .05
5	Control Thyroidex	40	110,689±7833	
	600 R at 48 Hr.	40	104,934±7932	> .05
	Control Thyroidex	36	74,752±5089	
	500 R at 48 Hr.	40	76,686±4116	> .05
	Control Thyroidex	26	61,742±3625	
	600 R at 48 Hr.	37	75,477±3482	.005
	Control Thyroidex	39	98,517±5709	
	600 R at 48 Hr.	39	92,514±6594	> .05
	Control Thyroidex	39	104,246±6149	
	600 R at 48 Hr.	38	100,203±6194	> .05

TABLE II (CON'T)

Experiment No.	*Stress*	*No. of Eggs*	*Counts/min. Mean Value*	*P*
6	Control Adrenex	40	117,885±6483	
	200 R at 48 Hr.	38	141,118±5113	.005
	Control Adrenex	29	82,708±5631	
	400 R at 48 Hr.	36	94,718±4479	.05
	Control Adrenex	40	49,522±3027	
	600 R at 48 Hr.	40	65,819±3951	.005

1. Standard error of the mean.
Hypophyex = Hypophysectomized; Thyroidex = Thyroidectomized
Adrenex = Adrenalectomized;

TABLE III

EFFECT OF PLASMA FROM STRESSED RATS ON UPTAKE OF I^{131} IN CHICK EMBRYOS

7	Control	40	101,034±5315	
	Exercised 4 days	40	104,918±4477	> .05
	Control	38	94,156±4597	
	Exercised 5 days	40	87,419±3207	> .05
	Control	40	72,773±5184	
	Exercised 5 days	40	66,784±4495	> .05
	Control	39	77,692±4844	
	Exercised 6 days	37	90,329±4232	.05
	Control	40	97,924±5140	
	Exercised 6 days	40	96,839±5497	> .05
	Control	40	65,781±3857	
	Exercised 7 days	40	77,860±4257	.025
8	Control	40	116,251±4491	
	5°C for 7 days	39	115,833±3906	> .05
	Control	39	84,118±4825	
	5°C for 7 days	32	76,141±3436	> .05
	Control	40	84,215±4366	
	5°C for 25 days	39	91,480±3679	> .05
9	Control	40	60,700±4464	
	35°C for 1 day	40	74,138±4371	.025
	Control	38	87,066±5062	
	35°C for 2 days	36	87,858±5316	> .05
	Control	38	88,362±4135	
	35°C for 1 day	40	80,038±4289	> .05
	Control	40	69,726±5047	
	35°C for 2 days	40	63,097±4510	> .05
10	Control	40	69,253±2925	
	Starved 3 days	40	62,016±3348	> .05
	Control	40	96,990±3765	
	Starved 7 days	40	79,173±4720	.005
	Control	40	85,124±4850	
	Starved 7 days	40	68,475±4474	.01

In Experiment 6 post exposure plasma from adrenalectomized rats significantly increased the I^{131} uptake in every instance.

In Experiment 7 only the plasmas from one 6-day and the 7-day groups of exercised rats elicited a significant increase.

In Experiments 8 and 9 plasmas from rats exposed to abnormally cold or hot environments failed to elicit a significant increase in the uptake of I^{131} by the embryos except in one instance in the heat exposed groups.

In Experiment 10 plasma from rats starved for 7 days did elicit a significant increase whereas plasma from a 3-day group did not.

It should be pointed out that if all the batches of eggs used in these experiments had been exactly comparable, then the mean control values should all have fallen within a narrow range. Previous experience indicates that the following reasons are why they do not:

1. The iodine content of the mother's diet drastically effects uptake of iodine in the embryo. Dietary iodine may vary widely according to the kind of food fed—natural or synthetic—the amount, the source of the food, and the season of the year.

2. The size of the embryos often varies considerably from batch to batch. Bigger embryos take up more iodine.

3. While the age of all the embryos in any one batch is assumed to be the same, anatomical evidence often shows a variation as large as ¾ of a day among the embryos. The older the embryo the more I^{131} the thyroid takes up. A batch weighted with older embryos will show a larger mean control.

In any one pairing of a control and an experimental, the eggs were always from the same batch throughout all these experiments.

DISCUSSION

These data show that a stimulatory response is seen in the uptake of I^{131} by the thyroids of chick embryos when they are injected with plasma from rats, guinea pigs and rabbits exposed to whole-body x-irradiation. The data also show that the time of post exposure bleeding is critical to the elicitation of the response. Mateyko and Edelmann (3) showed that following whole-body x-irradiation the pituitary content of thyrotrophin in rats was significantly increased at 6 and 24 hours when they terminated their experiment. Previous studies (4) have actually shown that this stimulatory response can be elicited—but not with the same regularity—with plasma obtained 24 hours after exposure of rats to whole body x-irradiation.

No conclusions can be drawn from the rat data in regards to a threshold dose for this response as even at the lowest dose tested a response was obtained.

The data from the x-irradiated rats in which endocrine organs were extirpated show that the adrenal gland is not necessary for the response to take place, but that both the hypophysis and the thyroid do seem to be necessary for the response.

If the response is mediated via the pituitary *(vide infra)*, the reason for the failure of plasma from hypophysectomized animals to elicit an increase in I^{131} uptake in the thyroids of the chick embryos is self evident.

On the other hand the failure of plasma from thyroidectomized rats to elicit a response is not so apparent. However, Purves and Griesbach (5) have shown that in thyroidectomized rats the thyrotrophin content of the pituitary rapidly declines to very low levels. Since these rats were not exposed to x-irradiation for at least 1-2 weeks after thyroidectomy, it is conceivable that the failure to elicit a response in the chick embryo with their plasma reflects a low thyrotrophic potency in the pituitary at the time of bleeding after the whole-body x-irradiation.

The results from the rats subjected to violent exercise, and abnormal environmental temperatures are equivocal. Two factors may be contributing. First, the duration, and second, the intensity of the particular stress may have been such as to overwhelm the thyrotrophic potency of the pituitary or vice versa insufficient to influence it at all. Violent exercise has been shown to have no influence on thyroid activity (6). Money (7), moreover, points out that, while heat and cold have been shown to result in changes in thyroid function, the assumption that these changes relate directly to thyrotrophin content of the pituitary and/or its secretion is only circumstantial.

The finding that plasma from completely starved animals significantly depresses the I^{131} uptake in the chick embryo is in keeping with the finding that starvation depresses the pituitary content of thyrotrophin (8). However, lacking an assay of the plasma for thyrotrophin, the explanation that the starved rat rapidly loses its ability to maintain even normal levels of thyrotrophin is speculative.

In a previous study (9) the same stimulatory changes found in the uptake of I^{131} and/or in the histology of the thyroid in chick embryos injected with either bovine or avian thyrotrophin were also seen in the thyroids of chick embryos exposed to whole-body x-irradiation or injected with plasma from chick embryos previously exposed to whole-body x-irradiation. These findings were interpreted to mean that thyrotrophin was secreted into plasma as a result of the stress of whole-body x-irradiation.

As considered, the present data suggest no reason to change this interpretation.

SUMMARY

Plasma from rats, guinea pigs and rabbits exposed to whole-body x-irradiation when injected into 15 day old chick embryos elicits a significant increase in the I^{131} uptake of the thyroid.

The time post x-irradiation when the exposed animal is bled is critical to the elicitation of the phenomenon.

No threshold dose was determined in the rat for this phenomenon.

The thyroid and pituitary glands seem to be essential in order to elicit the response while the adrenal is not.

Plasma from rats subjected to the stress of violent exercise or abnormal environmental temperatures does not consistently elicit the phenomenon.

Plasma from starved rats causes a significant depression in the I^{131} uptake in the chick embryo.

ACKNOWLEDGMENT

The technical assistance of Anna E. Handler, B.S., is acknowledged.

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Announcement to Authors

Preliminary Notes

Space will be reserved in each issue of THE JOURNAL OF NUCLEAR MEDICINE for the publication of one preliminary note concerning new original work that is an important contribution in Nuclear Medicine.

Selection of the preliminary note shall be on a competitive basis for each issue. One will be selected after careful screening and review by the Editors. Those not selected will be returned immediately to the authors without criticism. Authors may resubmit a rejected or revised preliminary note for consideration for publication in a later issue. The subject material of all rejected manuscripts will be considered confidential.

The text of the manuscript should not exceed 1200 words. Either two illustrations, two tables, or one illustration and one table will be permitted. An additional 400 words of text may be substituted if no tables or illustrations are required. Only the minimum number of references should be cited.

Manuscripts should be mailed to the Editor, Dr. George E. Thoma, St. Louis University Hospital, 1325 South Grand Blvd., St. Louis 4, Missouri. They must be received before the first day of the month preceding the publication month of the next issue, e.g., preliminary notes to be considered for the September, 1963 issue must be in the hands of the Editor before August 1, 1963.

JOURNAL OF NUCLEAR MEDICINE 4:320-325, 1963

Importance of Stop Flow to Kidney Scans[1,2]

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New Orleans

INTRODUCTION

It is well known that obstruction of the ureters frequently results in a nephrogram effect during the conventional intravenous pyelogram. If the obstruction is for a short period of time, the effects on the kidney are almost completely reversible. (3, 5) It therefore occurred to us that by blocking the ureters we could possibly achieve scans of the kidney depicting the parenchymal portions of the kidney, without the overlap of the calyces or pelvic portions. This method could then be used to identify small areas of non-functioning renal tissue.

In order to effect ureteral blocking and hence "urinary stop-flow", it is necessary to insert ureteral catheters large enough to prevent leakage around the catheter. The procedure is performed on a cystoscopy table and the catheters are connected to a pressure transducer recording system which also effectively results in blocking the ureteral catheters. The increasing intrapelvic pressure results in cessation of urine formation. This occurs at about 60 to 80 millimeters of mercury. However, tubular activity may continue to change the concentration of various solutes in the intratubular urine. (6, 8)

If a radioactive compound is used which is known to be actively secreted by renal tubules, the radioactive material concentrates in normal tubules in amounts that are a function of the tubular blood flow. Since the radioactive material is retained as long as urine flow remains blocked, the total dose of administered radioactivity can be reduced. This procedure also results in lower body background, since the radioactivity builds up within the kidneys in a short period of time.

EXPERIMENTAL APPROACH

Previously we reported our results in dogs. (2) In these experiments we

[1]From: The Department of Surgery; Division of Urology, and Department of Radiology, Tulane University School of Medicine.

[2]Supported in part by U. S. Public Health Grants (H-4659 and C-4581).

[3]Presented at the 9th Annual Meeting of the Society of Nuclear Medicine, Dallas, Texas, June 27-30, 1962 by Doctor Izenstark.

found that there was sufficient concentration within the kidneys to permit scanning within three to five minutes after injection of the radioactive material under stop-flow conditions. Concentration in the kidneys was six to twelve times that of other organ areas. Once stop-flow was released the first few cubic centimeters of urine collected from the renal pelvis was free of radioactivity, thereby confirming that urine flow had indeed ceased.

The dog experiments involved the production of ischemic areas within the kidneys followed by scans, and interpretation of the scans by an individual unfamiliar with the procedure performed. In all cases it was possible to correctly interpret the scan.

Since reporting our initial work we have studied five additional dogs with regard to the actual renal concentration and localization of radioactive o-iodohippurate under the conditions of stop-flow. After establishing the conditions of stop-flow and injecting I^{131} labelled o-iodohippurate into the dog, one kidney was removed and immediately frozen in acetone and dry ice. Various parts of this kidney were dissected and small aliquot portions counted for radioactivity in a well-counter. Meanwhile, stop-flow was released on the kidney which was allowed to remain in the animal. After allowing a time lapse for urine flow, this kidney was similarly removed from the animal, frozen and dissected. The tissue from this second kidney was also counted in a well-counter.

Analysis of the results (4) from the above procedure showed significantly higher concentrations of radioactive material in the cortex during stop-flow, than in the papilla, medulla, or plasma. This finding would be expected with a substance actively secreted by the proximal tubules. The levels of radioactivity found in the medulla and papilla were comparable to that of the plasma.

In the kidneys removed after stop-flow was released the concentration of radioactive material is of the same level in the papilla, medulla, and cortex.

These findings indicate that the renal scans obtained under stop-flow conditions are of the cortical areas rather than of the medulla. When stop-flow is not used the urine concentration of radio-o-iodohippurate is approximately ten fold that of the renal parenchyma. The presence of such highly radioactive urine in the pelvis and calyces may obscure small areas of decreased uptake, making scans with radio-o-iodohippurate without the use of stop-flow of questionable value. This would be particularly true in the diagnosis of small areas of ischemia or parenchymal disease.

The method used above can be used to evaluate other drugs secreted by the kidney. We are currently studying the localization of $Mercury^{203}$ labelled Chlormerodrin. Preliminary results (Table I) show that this material is also concentrated in the cortex of the kidney both before and after the application of stop-flow. Unlike o-iodohippurate, there is no shift of concentration in the medulla or medullary papilla indicating that the material remains fixed in the cortical areas of the kidney. Twenty-four hours after injection of Chlormerodrin, the concentration in the kidneys is significantly higher than in the serum. However, there is still radioactivity in the urine both before and after stop-flow, indicating that there is still some unbound Chlormerodrin present after twenty-four hours and that the material is not all completely bound in the tubules.

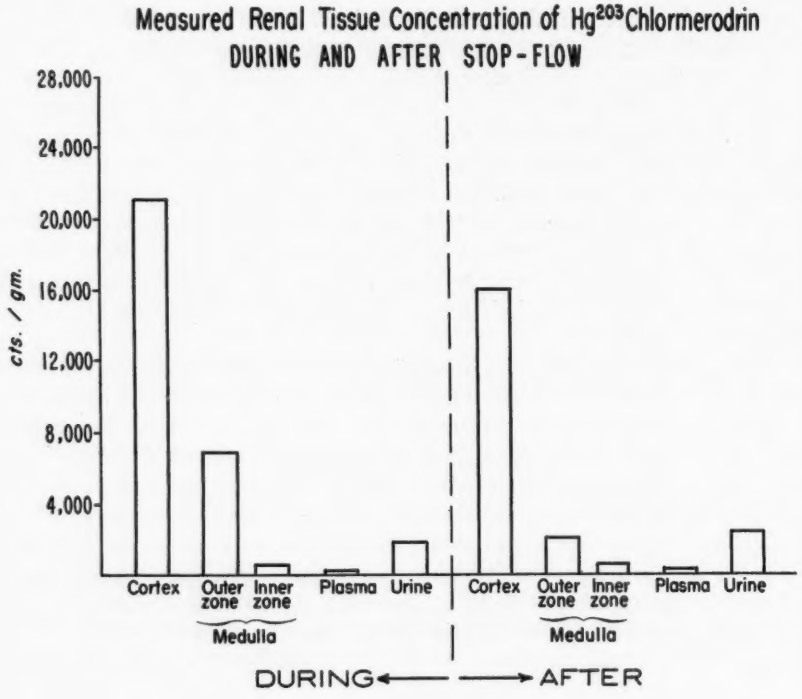
PATIENT SCANS

We have now performed stop-flow kidney scans on twelve patients with various renal abnormalities. No patients with acute infection or uremia were selected. Initially, we thought that in order to achieve satisfactory concentration of radioactivity within the kidneys, it was necessary to produce obstruction of both ureters. However, in some of our patients there was leakage about the catheters and yet we were able to obtain satisfactory o-iodohippurate scans. We are now catheterizing and blocking only the ureter on the side of interest and obtaining satisfactory scans (Fig. 1). Compensating for the loss of radio-o-iodohippurate through the other kidney, constant intravenous infusion of radioactive o-iodohippurate is maintained.

In order to assure high urine volume, intravenous infusion of 8 per cent urea and 5 per cent dextrose in water is given prior to the introduction of the catheters. Number eight disposable polyethylene catheters are used. The transducer pressure plateau indicating cessation of urine formation is reached in five to ten minutes, depending upon the urine volume. We have used doses of 100 to 200 microcuries of radioactive o-iodohippurate (I^{131}) injected intravenously. It is our

TABLE I

CONCENTRATIONS OF CHLORMERODRIN (Hg^{203}) IN DOG'S KIDNEYS BEFORE AND AFTER STOP-FLOW, TWENTY-FOUR HOURS AFTER INJECTION OF 100 MICROCURIES.



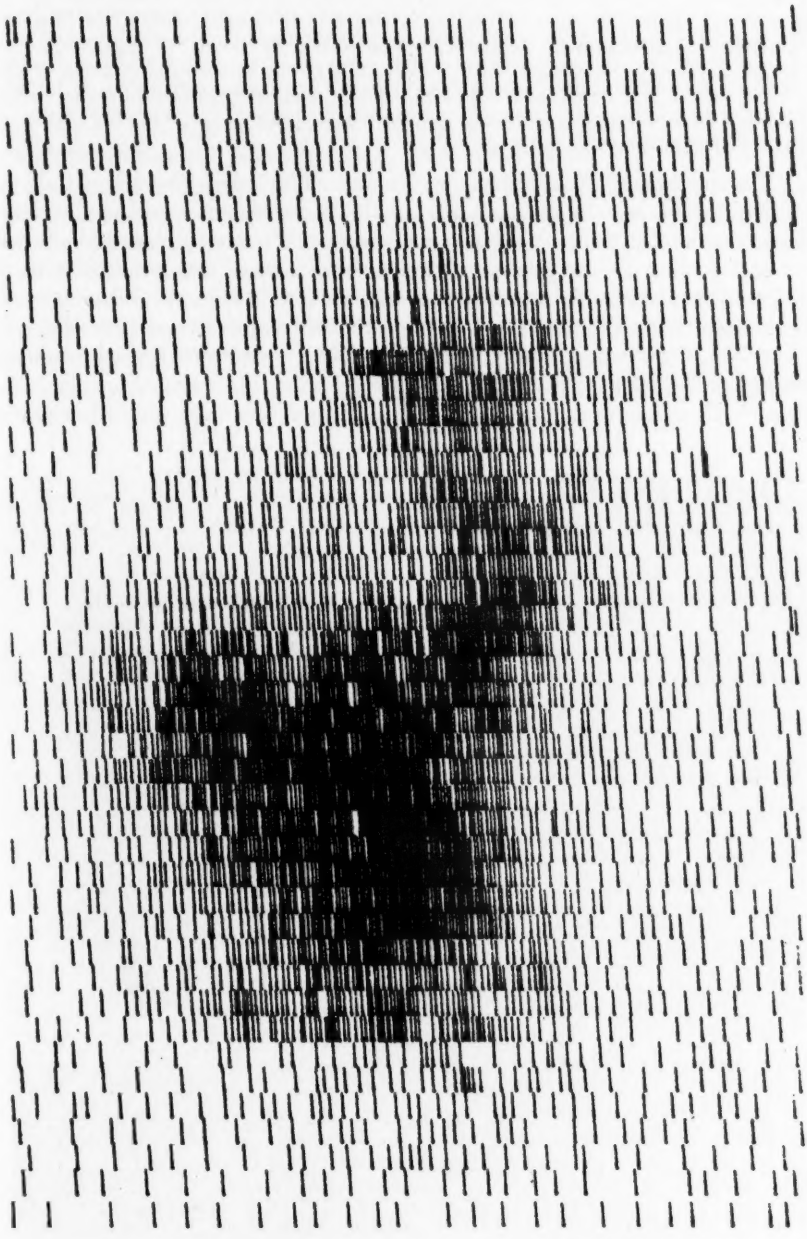


Fig. 1. (A) Scan of right kidney demonstrating absent uptake in upper pole.

opinion that with better collimation of our scanning equipment this dose could be reduced. However, it nevertheless is still less than that which has been reported in the literature by other investigators. (1, 7)

Since it was desirable to scan patients on the cystoscopy table, it became necessary to modify our scanning equipment to permit the scanning probe to pass over the cystoscopic table. (2)

The production of stop-flow as we are currently performing it is not always practical for several reasons. First, it is not always possible to introduce the catheter into the ureter. In some patients when the catheter is in place leakage will still occur. Secondly, the process of catheterization sometimes requires as much time as that saved by the reduced time of scanning. Thirdly, stop-flow is somewhat uncomfortable to the patient although this discomfort can be controlled with drugs. Fourthly, the passage of a large size catheter necessitates special consideration in handling of the patient following the procedure. In order to overcome the ureteral edema we continue our patients on 4 per cent urea for forty-eight to

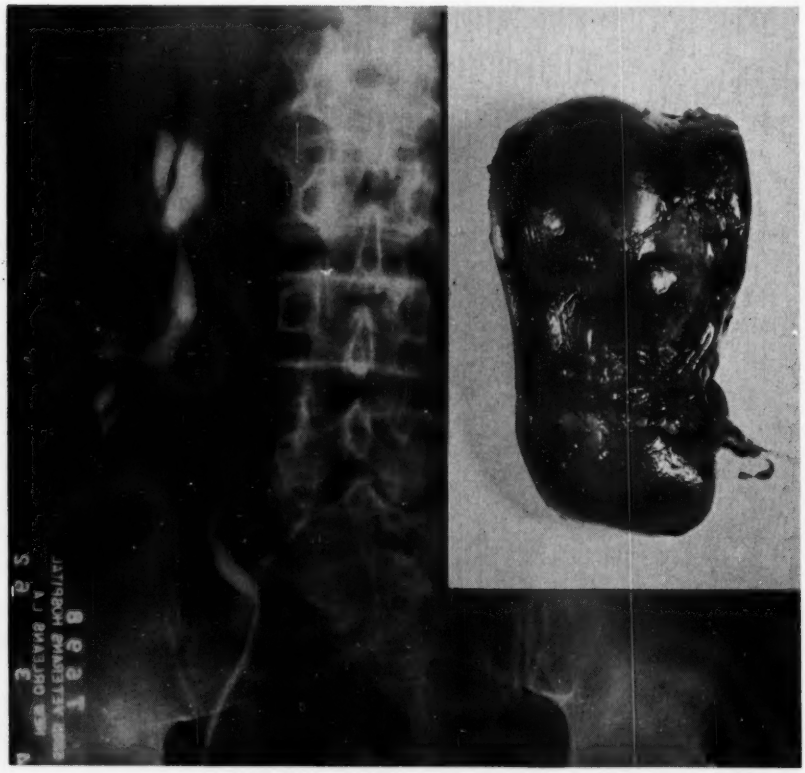


Fig. 1. (B) Radiograph of same patient with insert of pathological specimen which proved to be a benign cyst.

seventy-two hours. This means additional hospitalization for the patient. However, we have observed no severe reactions following the procedure.

By combining unilateral stop-flow with intravenous infusion of radio-o-iodohippurate the problem of ureteral catheterization with a large catheter is minimized. Despite the fact that technical difficulties may make it impossible to obtain stop-flow in some patients, the quality of the scans and the rapidity with which the radioactive o-iodohippurate is eliminated once stop-flow is released, makes this method useful. The very high concentration of radio-o-iodohippurate during stop-flow in the renal cortex against the very low concentration in blood, urine, renal medulla and other organs permits a resolution not presently available with other methods currently in use.

Mercury^{203} Chlormerodrin has been suggested for use to obtain cortical scans. If scans are performed twenty-four hours later there is little radioactivity in the urine, and the material is concentrated in the cortical areas. The disadvantage, however, is that the radioactivity is not eliminated, except by physical decay.

SUMMARY

Stop-flow renal scanning offers a method of achieving kidney scans of improved quality with lower radioactive o-iodohippurate doses. Equally important is the fact that this method is useful to study the exact localization of drugs within the kidney.

We recognize that there are several disadvantages to the procedure of stop-flow although we have observed no serious reactions in our small series of patients. These disadvantages can be minimized by attention to physiological principles.

ACKNOWLEDGEMENTS

We wish to express our appreciation to Dr. Paul Numerof of E. R. Squibb and Sons for graciously supplying us with Mercury^{203}-Chlormerodrin. Also to Mrs. Mary Cazalas and Mr. Raymond Washington for their technical assistance.

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JOURNAL NUCLEAR MEDICINE 4:326-330, 1963

PRELIMINARY PROGRESS NOTE[1]

Localization of Brain Tumors with the Positron Scintillation Camera[2,3]

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Berkeley, California

This report describes the first clinical use of the positron scintillation camera to localize brain tumors. The instrument is a variation of the scintillation camera (1) for imaging the distribution of positron emitting isotopes. The isotope used in Gallium^{68} with a half life of 68 minutes. The radiation dose to the patient is much lower than with other methods of brain tumor localization, and the pictures are obtained in a relatively short time.

POISTRON CAMERA

An earlier version of the positron camera has been described. (2) It makes use of a stationary image detector and coincidence detector to produce images without the use of collimators or mechanical scanning. It has recently been modified by the use of an 11½-inch diameter by ½-inch thick image-detector crystal. This large crystal permits taking pictures of the entire brain with one exposure. Moreover, a compound coincidence detector consisting of 19 scintillation counters with crystals 1¾ inch in diameter by 2 inches thick is now being used. With these changes in the instrument, very high sensitivity is obtained, and relatively sharp focus is maintained on a predetermined plane in the subject. Concentrations of activity on this plane are in sharpest focus, while activity on other planes is less sharply defined. The depth of the plane of best focus can be set by electronic means.

The sensitivity is such that 1 microcurie of the isotope used in these studies produces about 500 dots per minute on the picture, when the isotope is located at the center of a phantom equivalent to a subjects head. This is approximately 20 times the average counting rate per microcurie obtained when scanning Hg^{203} with a 19-hole focused collimator under the same conditions. Moreover, better resolution and lower background are obtained. A forthcoming publication will describe the instrument in detail.

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[1]Preliminary Progress Note, see page 305 and 319.

[2]Work done under the auspices of the U. S. Atomic Energy Commission.

[3]Lawrence Radiation Laboratory and Donner Laboratory of Medical Physics and Biophysics, University of California, Berkeley, California.

RADIOIOSTOPE COMPOUND

The agent used for brain tumor localization is Gallium^{68}-EDTA obtained from the Germanium-Gallium cow as described by Gleason (3) and modified by Green and Tucker. (4) The parent isotope Ge^{68} has a half life of 275 days. The daughter Ga^{68} decays by positron emission 85 per cent of time and has a half life of 68 minutes.

The pharmacology of Carbon^{14}-labeled $CaNa_2$ EDTA has been studied by Foreman. (6) He showed that immediately after intravenous administration of EDTA to rats, about 80-90 per cent of the material passed rapidly out of the vascular system and into equilibrium with what is presumed to be extra cellular space. The biological half time of the remaining material in the blood for both man and rats is approximately 1 hour. The principle route of elimination is by the kidneys. In man over 95 per cent is excreted in 24 hours.

Our studies of the distribution of Ga^{68}-EDTA in the rat show no significant differences in distribution and excretion when compared to Foreman's findings. None of the organs, including the liver, appeared to concentrate the material to any extent. The stability constant of Ga^{68}-EDTA is higher than Cu^{64}-EDTA, which has been used for brain tumor localization by Bagnall, *et al.* (5) Measurement of urinary excretion of Ga^{68}-EDTA in several of our patients showed half times similar to those found by Foreman.

Our studies in the rat showed approximately 0.05 per cent of the dose in the brain 1 hour after intravenous administration. Furthermore, Foreman showed in man that the concentration of EDTA in the spinal fluid was only 1/40 that of the plasma under the same conditions. This indication of exclusion by the intact blood-brain barrier provides the rationale for the use of labeled EDTA in brain tumor localization in situations where increased permeability of the blood-brain barrier exists.

TECHNIQUE

The usual amount of the isotope given to a patient is 250 microcuries. The whole-body radiation dose estimated on the basis of uniform distribution is less than 7 millirad, and the renal dose, as estimated by *in vivo* counts over the kidneys, is less than 50 millirad.

After obtaining the labeled solution from the positron cow, it is passed through a Millipore filter of 0.22 micron pore size for sterilization, thus saving the time needed for autoclaving. The examination is usually started by taking frontal views with the patient in the face-up or face-down position. Small positron-emitting marker sources are taped over each external auditory canal to permit anatomic orientation of the patient in the scintiphoto. Immediately after injection of the isotope, 1-minute scintiphotos are taken to check the positioning of the patient. Then a longer exposure, usually lasting 10 minutes, is made. Lateral views are also obtained. For these the marker sources are placed at the lateral edge of the eye, the lower margin of the ear, and the external occipital protuberance.

The determination of where to set the plane of best focus depends on the individual patient. If there are obvious clinical signs, the plane is set through the suspect area. Otherwise, the plane of best focus is set at a depth of 2 to 3 inches and four views are taken—face-up, face-down, right lateral, and left lateral.

Because of the short waiting period after administration of the isotope and the rapidity with which the positron scintiphotos are obtained, the examination is completed in a relatively short time. Sometimes, a picture of diagnostic value is obtained only 10 minutes after injection of the isotope. The time from the moment the patient enters the clinic until he leaves is about 2 hours, and this includes the time necessary to obtain the isotope from the positron cow.

ILLUSTRATIVE CASES

The patient shown in Figure 1 had a craniotomy 1 year before this examination with subtotal resection of a left midline meningioma. The frontal scintiphoto shows a large recurrence in the midline, this time predominantly on the right side. Surgery confirmed the location of the tumor. The marker sources at the

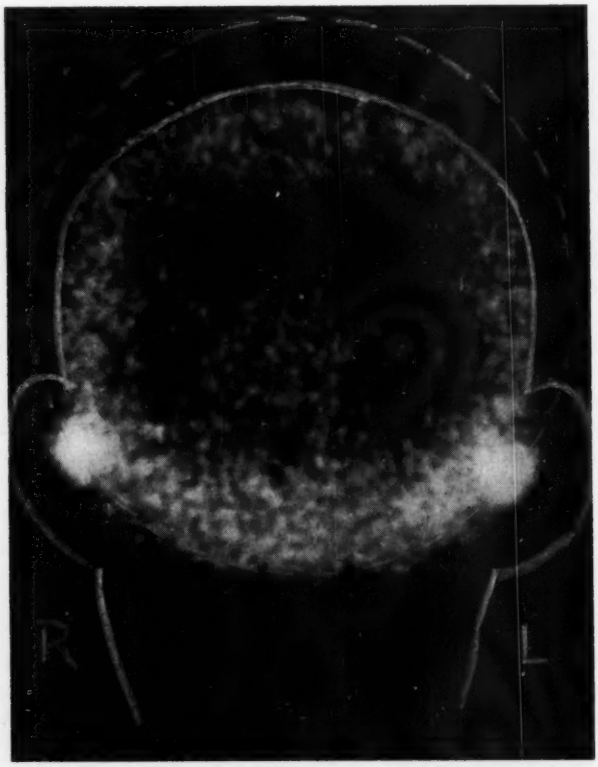

Fig. 1. A 10-minute positron scintiphoto taken with Ga^{68}-EDTA. This frontal view shows a large midline meningioma.

ear canals are visible at the lower right and left of the picture. The outline of the head is visible because of uptake of Ga^{68}-EDTA in the skin and diploe. The limit of the field of view of the positron camera is indicated by the dashed circular line.

The patient shown in Figure 2 had a 7-month history of bitemporal hemianopsia. The left lateral scintiphoto shows an area of abnormal uptake posterior to the eye marker in the region of the sella turcica. A Hg^{203} Neohydrin scan was interpreted as being normal and, even in retrospect, was but faintly suggestive. The subsequent craniotomy revealed a walnut-sized chromophobe adenoma.

DISCUSSION

At the time of this writing, positron scintiphotos have been taken on more than 25 patients. Of these subjects, seven have also had photoscans with Hg^{203} Neohydrin. In four cases, tumors were visible on both the Hg^{203} scans and on the positron scintiphotos. In two cases, masses have been evident on the positron scintiphotos when they were not identified on the Hg^{203} scan. Both of these were

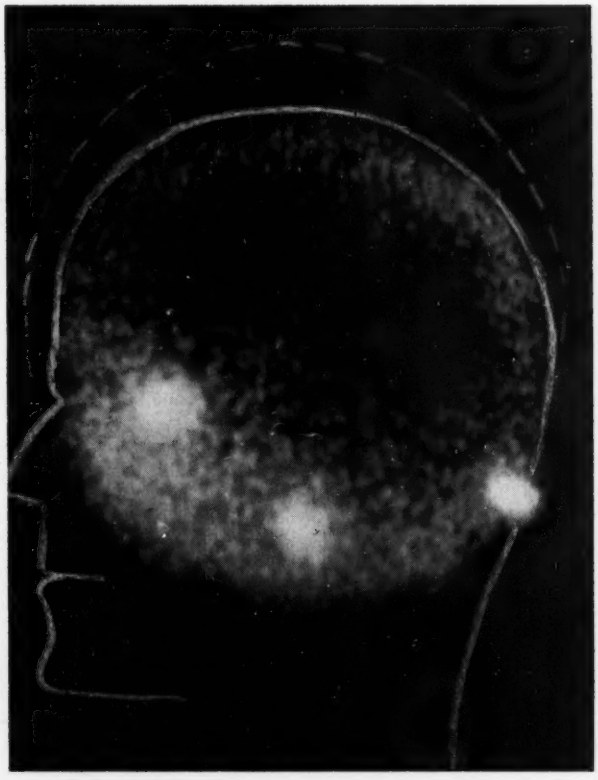

Fig. 2. A 10-minute lateral positron scintiphoto demonstrating an area of abnormal uptake posterior to the eye marker in a patient with a chromophobe adenoma of the pituitary.

pituitary lesions. One, a chromophobe adenoma, was confirmed surgically. The other had corroborative pneumoencephalographic findings. In one case, neither method localized the tumor, a solid astrocytoma of the left fronto-temporal area.

The interpretation of positron scintiphotos obtained with EDTA is more difficult than photoscans obtained with Neohydrin. This is partly due to the uptake of EDTA in the skin and diploe surrounding the brain, because tumors must contain enough activity to be seen over this apparent background. This disadvantage is at least partly overcome by the high sensitivity of the positron camera because it records a larger number of dots on the picture per microcurie in the subject and thus gives pictures that have good statistical reliability.

This technique of localizing brain lesions may be applicable on a large scale as a screening procedure. The radiation dose to the patient is minimal, the time of examination is short and, except for the intravenous injection, no discomfort is produced. With the use of the positron cow, the Ga^{68}-EDTA is readily available and is inexpensive, because hundreds of doses of the isotope can be ob-obtained before the parent isotope has decayed. Since the Ga^{68} has such a short half life, an examination can be repeated or other isotope studies done the following day if desired, and only minimal precautions are necessary in handling the isotope.

ACKNOWLEDGEMENT

Acknowledgement is extended to Doctors John E. Adams and Kenneth R. McCormack, of the University of California Medical Center, San Francisco, California, for furnishing the patients shown in these studies, and to Mr. Phillip Yost and Mr. Yukio Yano for technical assistance.

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CURRENT ABSTRACTS IN NUCLEAR MEDICINE

CALIBRATION AND STANDARDIZATION OF THYROID RADIOIODINE UPTAKE MEASUREMENTS.

Acta Radiologica **58**:233, 1962.

In 1960 the International Atomic Energy Agency sought the advice of a number of well-known specialists to suggest a standardized procedure to ensure comparability of thyroidal radioiodine uptake measurements. This report summarizes the unanimous recommendations of the group, together with some comments on the reasoning behind the recommendations. Their opinion was that not more than 10μc. of I-131 need be given, except for thyroid scanning where a dose of 50 μc. might be necessary. In a normal person, the 10 μc. dose results in a radiation dose of between 5 and 20 rads to the thyroid gland. The amount of I-127 in each dose should not exceed one μg. The use of a neck phantom is essential; the thigh should not be considered as representative of a human athyreotic neck; the crystal size should not be less than 2.5 $\times$ 2.5 cm; the 90 per cent isoresponse line should extend over a field between 12 and 15 cm in diameter; and the side and back shielding should be adequate. In most circumstances, a distance of between 20 and 30 cm from the surface of the detector to the isthmus of the gland is recommended. The use of a spectrometer is not essential but may be usefully employed to reduce background and for energy selection. The statistical error should be less than three per cent.

Probably no human endeavor provokes more criticism than an attempt to standardize a technical procedure. That the consultants were aware of this is evidenced by the great variability that they considered permissible. A specific example of vagueness is the statement that "the so-called early uptake tests are likely to provide information of greater diagnostic significance than 24 hour or 48 hour uptake measurements," without specifically mentioning the effect on the 24 hour uptake of rapid release of radioiodinated thyroxine from the thyroid of a hyperthyroid individual. Other weaknesses are the description of the recommended collimators, the inadequate discussion of spectrometry in any detail, and the neglect of specifications of the radiochemical purity of the iodine preparations. In summary, the attempt at standardization was well conceived, but failed to extend significantly the previous efforts of Marshall Brucer to standardize measurement of thyroidal uptake of radioiodine.

Abstracted by Henry N. Wagner, Jr., M.D., Johns Hopkins Hospital, Baltimore.

REVIEW ARTICLE: SELENIUM ANALOGUES OF BIOLOGICALLY ACTIVE SULPHUR COMPOUNDS.

DINGWALL, D.: *J. Pharmacy & Pharmacology* **15**:765, 1962.

The discovery that a factor containing selenium is an essential dietary constituent for rats has resulted in increased interest in the synthesis and biological activity of selenium analogues of sulphur compounds.

Selenium analogues for the following sulphur compounds have been synthesized and studies—(1) selenopantethine, used by Lactobacilli in the biogenesis of coenzyme A; (2) selenium analogues of sulfonamides and sulphones; (3) seleno-amino acids, such as selenocystathione, methylselenocysteine, selenocysteine, selenomethionine, and homocystine; (4) strongly antibacterial selenium derivatives of chloramphenicol; (5) selenium analogues of thiosemicarbazides which have anti-tuberculan and anti-fungal activity; (6) many purine and pyramidine derivatives. Some of these, such as 6-selenopurine, are unstable, while others, such as 6-selenoguanine, are stable and are being investigated for anti-tumor activity. (7) 2-selenobarbituric acid derivatives; (8) selenium analogues of promethazine and chlorpromazine with good anti-histaminic activity, (9) selenocystamines, selenohypotaurine, and selenotaurine and (10) long chain fatty acids containing selenium.

Present knowledge of the site of localization of selenium compounds in the body is still limited. However, incorporation of selenium-containing amino acids into proteins has been demonstrated. Frequently, excretion of selenium analogues is quite similar to the sulphur compounds.

Abstracted by J. C. McAfee, M.D., Johns Hopkins Hospital, Baltimore.

MULTIPLE-ORGAN CANCER SCREENING WITH DIAGNOSTIC RADIOAUTOGRAPHIC PROCEDURES.

ACKERMAN, N. B., MCFEE, A. S., BLUM, J. A., MAKOWSKI, E. L., AND WAGENSTEEN, O. H.: *J.A.M.A.* 183:122 (Jan. 5) 1963.

The authors review their experience with *in vivo* cancer diagnosis using radioautography after intravenous injection of P^{32}. X-ray film is applied over easily accessible body areas (skin, breast), or a rubber balloon coated with a photosensative emulsion is positioned in less accessible areas (esophagus, stomach, rectum, bladder, cervix). The film or balloon is left in place for periods up to 24 hours and then developed. A more intense contrast on the film suggests malignancy. ~more intense than what??

Although results are preliminary—and include a considerable number of false-positives and false-negatives—they are both promising and suggestive. The technique has advantages over Geiger-Muller counting, being more sensitive, reducing errors in counting statistics, and being able to screen large areas of the body for P^{32} activity. Less available areas of the body mav eventually yield to this method if appropriate tagged materials are found.

Abstracted by Robert A. Nordyke, M.D., Straub Clinic, Honolulu.

THE MEASUREMENT OF GAMMA EMITTING ISOTOPES IN FECES.

CLAPHAM, W. F. AND HAYDER, C. J.: *Phys. in Med. & Biol.* 7:313, 1962.

A simple convenient scintillation counting system is described for counting of radioactivity in fecal samples. No sample processing is required. The scintillators consist of plastic phosphors 5 inches in diameter and 3 inches thick coupled to matched 5 inch photomultipliers. The unit, of 350 ml capacity, provides counting data independent of volume over a range of 1-350 ml.

Sensitivities reported are:

Isotope	*cts/sec/μc*	*Background cts/sec.*
Ca-47	3300	20
Cr-51	340	20
Co-58	2800	13
Fe-59	2800	10
Br-82	7000	13
I-131	3800	17

Abstracted by Paul Numerof, Sc.D., E. R. Squibb & Sons, New York.

ANGIOTENSIN LABELLED WITH I-131 AND WITH TRITIUM

BARBOUR, B. H. & BARTTER, F. C.: *J. Clin. End. & Metab.* 23:313, 1963

A basic principle of tracer methodology is to establish with certainty chemical and biological purity of the labeled material under investigation. Yet even today, one can still observe

violations of this principle which at best have led to a considerable waste of the investigators' time and at worst to the dispersal of a lot of misinformation. This paper points out that when synthetic angiotensin was iodinated by previously accepted techniques, marked chromatographic differences were observed between the original angiotensin and the labeled product. Virtually all the radioactive material was biologically inactive when bioassayed. While tritiated angiotensin had a single chromatographic peak (slightly different from the starting material) that retained biological activity, the latter was reduced to one-eighth of the original potency. The authors conclude that published reports indicating significant differences in the volume of distribution and degradation rates of angiotensin between normal and hypertensive subjects, are subject to the criticism that they were derived from the use of angiotensin I-131. The biological purity of tritiated angiotensin remains to be proved.

Abstracted by H. N. Wagner, Jr., M.D., John Hopkins Medical Institutions, Baltimore.

THYROID CARCINOMA IN MAN AFTER EXPOSURE TO IONIZING RADIATION A SUMMARY OF THE FINDINGS IN HIROSHIMA AND NAGASAKI

SOCOLOW, E. L., HASHIZUME, A., NERIISHI, S., AND NIITANI, R.: *N.E.J.M.* **268**:406, 1963

A unique opportunity to study the development of thyroid carcinoma in man after exposure to ionizing radiation comes from the atomic explosions at Hiroshima and Nagasaki in 1945. During a three-year study carried out by the Atomic Bomb Casualty Commission (1958-1961) routine medical examinations were done on about 19,000 individuals. Enlarged thyroid glands were found in 355 cases. One hundred thirty-one individuals were recommended for biopsies without knowledge of the patient's exposure status. Twenty-one cases of thyroid cancer were found, 14 of which occurred in persons within 1,400 meters of the hypocenter. Sixteen of these were females and five were males. Age at the time of the bombing ranged from 7 to 52 years with a mean of 26.2. Only two cancers were found in the matched, non-exposed group.

This significant increase in the development of thyroid carcinoma in the heavily irradiated group—regardless of age at time of irradiation—has occurred 13 to 16 years after exposure. Subsequent examination of the same matched groups will be watched with extreme interest.

Abstracted by Robert A. Nordyke, M.D., Straub Clinic, Honolulu.

SIMPLE METHOD FOR THE DETERMINATION OF PLASMA CORTICOIDS

MURPHY, B. P., ENGELBERG, W. & PATTEE, C. J.: *J. Clin. Endocrino. & Metab.* **23**:293, 1963

This is another example of a technique that requires a radioisotopically labelled agent. A similar principle referred to as "saturation analysis" has been used previously to measure plasma levels of vitamin B 12. The addition of increasing amounts of a hormone (cortisol) to an equilibrium dialysis system containing standard plasma and a constant amount of labelled hormone (cortisol-4-C-14) causes a proportional decrease in the percentage of the labelled hormone bound to the plasma protein. If one frees endogenous cortisol from the plasma globulin to which it is bound in an unknown plasma sample, the cortisol content can be determined by comparison with a standard curve. The method gave a standard deviation of one microgram over the range of 0 - 10 micrograms/100 milliliters. Values obtained in this paper were similar to those obtained using the method of Nelson and Samuels. The mean recovery of cortisol added to plasma was 91 per cent.

Abstracted by Henry N. Wagner, Jr., M.D., Johns Hopkins Medical Institutions, Baltimore.

CALENDAR OF EVENTS

Date		
August, 1963		
9-15	6th International Congress of Nutrition including Symposium on Balance Experiments and Isotopes in Nutritional Investigations	Edinburgh, Scotland
20-23	2nd International Pharmacological Congress, including papers on the Use of Isotopes and on Radiation Protection	Prague, Czechoslovakia
26-30	Symposium on Radiological Health and Safety in Nuclear Materials	Vienna, Austria
26-30	Technical Meeting on Radioisotopes in the Biochemistry and Physiology of Milk Secretion	Copenhagen, Denmark
26-31	9th Congress of the European Society of Haematology including Section on the Use of Radioisotopes in Haematology	Lisbon, Portugal
September, 1963		
6-7	Meeting of the Nuclear and Radiation Chemistry Technical Group of the German Chemical Society	Karlsruhe-Leopoldshafen, Germany
19-20	International Conference on the Industrial Applications of Radioisotopes	Zurich, Switzerland
October, 1963		
1-4	Annual Meeting of the American Roentgen Ray Society	Montreal, Canada
7-11	Symposium on Biological Effects of Neutron Irradiations	Vienna, Austria
17-19	Southeastern Chapter—Society of Nuclear Medicine	Bal Harbor, Florida
21-25	Seminar on Medical Radiation (Limited Attendance)	Ottawa, Ontario, Canada
November, 1963		
17-22	Radiological Society of North America	Chicago, Illinois
18-21	Joint Winter Meeting of the American Nuclear Society and the Atomic Industrial Forum and Atom Fair	New York, New York
19-21	Meeting of the American Physical Society	Norman, Oklahoma
December, 1963		
19-20	Symposium on Radiation Emergencies in Medicine, Research, and Industry	Chicago, Illinois
January, 1964		
	6th International Symposium on Radioactive Isotopes in Clinical Medicine and Research	Bad Gastein, Austria
February, 1964		
5-8	American College of Radiology	Tucson, Arizona
March, 1964		
20-22	Southwestern Chapter, Society of Nuclear Medicine	Houston, Texas
April, 1964		
13-16	Annual Meeting of the American Radium Society	White Sulphur Springs, West Virginia
June, 1964		
17-20	*11th Annual Meeting of the Society of Nuclear Medicine*	*Berkeley, Calif.*
August, 1964	8th Inter-American Congress of Radiology	Caracas, Venezuela
June, 1965		
16-19	*12th Annual Meeting of the Society of Nuclear Medicine*	*Bal Harbour, Florida*

This Calendar of Events will contain basic information on special courses and meetings of interest to members of The Society of Nuclear Medicine. If you desire more complete information, Mr. Samuel N. Turiel, Administrator of The Society will be pleased to supply you with the name and address of the convening body or sponsoring organization, upon receipt of your request.

JOURNAL OF NUCLEAR MEDICINE 4:335-344, 1963

A New Scanning Isotope, Mercury^{197} A Preliminary Report[1]

D. Bruce Sodee, Major, MC

Brain and renal photoscanning with mercury^{203} Neohydrin has recently been popularized. However, mercury^{203} Neohydrin has a major disadvantage as a scan agent due to its long physical half-life of 47 days and its renal radiation dose of approximately 48 rads. For this reason, we have investigated another isotope of mercury, mercuric^{197} chloride, which has a 99 per cent gamma emission of .077 mev and a half-life of 2.7 days.

PROCEDURE

Radiation dosimetry was calculated, utilizing the standard formulas of Quimby (1). Photoscanning was performed with two unmodified Picker magnascanners. The radiochemical mercuric^{197} chloride ($Hg^{197}Cl_2$) was obtained from a commercial source sterile and pyrogen free.

RESULTS

Physical Characteristics of Mercury^{197}:

Mercuric^{197} chloride is produced by bombardment of mercury^{196} with a neutron source. The isotope is composed of mercury^{197M} which has a half-life of 23 hours (beta energy of .165 mev, gamma energy of .275 mev, .165 mev, and .135 mev) and mercuric^{197} chloride with a physical half-life of 2.7 days (no beta, 99 per cent gamma emission of .077 mev, one per cent, .190 mev) (Fig. 1). The isotope was utilized five days after production to minimize the mercury^{197M} concentration. The mercury^{203} contamination was less than 2 per cent.

Biological Characteristics of Mercury^{197}:

Following intravenous administration of 100 microcuries of mercuric^{197} chloride, plasma clearance and chloride excretion patterns were plotted (Figs. 2 and 3). The plasma clearance one-half time of the mercuric^{197} chloride was six

[1]Isotope Section, Radiology Service, Walter Reed General Hospital, Walter Reed Army Medical Center, Washington 12, D.C.

TABLE I

COMPARISON OF MERCURY^{203} NEOHYDRIN AND MERCURY^{197}

	Mercury^{203} Chloromerodrin	*Mercury^{197} Chloride*
Physical $t_{1/2}$	48 d	2.7 d
Effective $t_{1/2}$ body	0.5 d	1.16 d
kidney	18 d	1.16 d
β energy	0.21 mev	———
γ energy	.280 mev	.077, .191 mev
RADIATION DOSE/100 uc		
Whole body	.003 rad	.013 rad
Liver	.04 rad	.02 rad
Spleen	———	.077 rad
Kidneys	10 rad	———
		5 rad

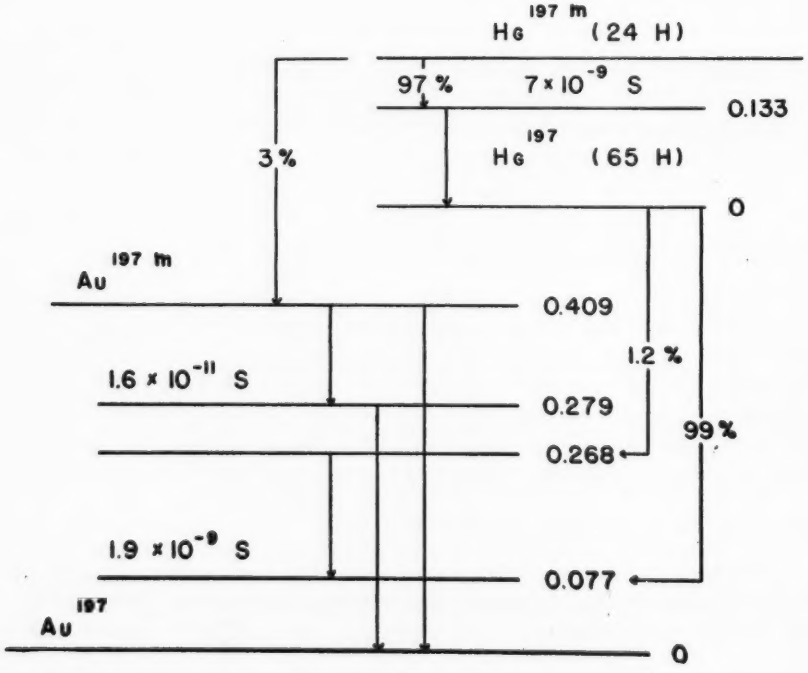

Fig. 1. The disintegration scheme of mercury^{197} and its isomer mercury^{197M}.

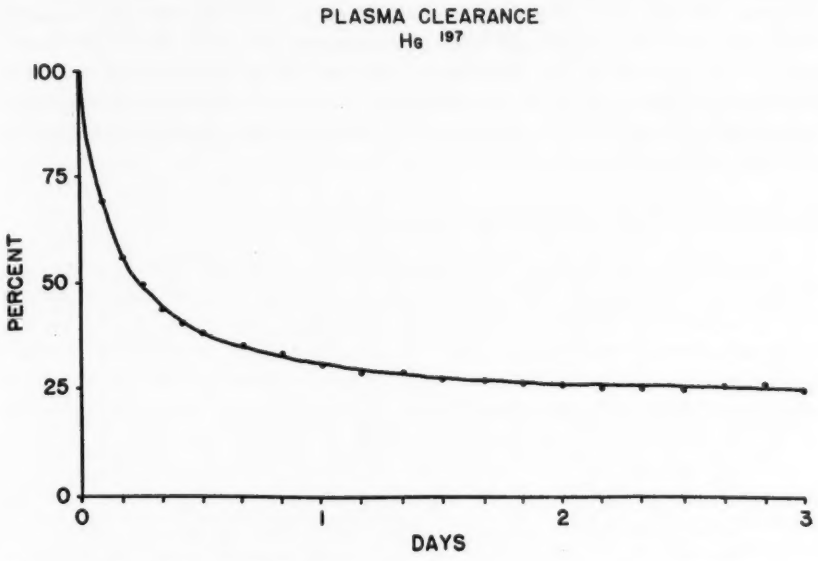

Fig. 2. The plasma clearance of mercury[197].

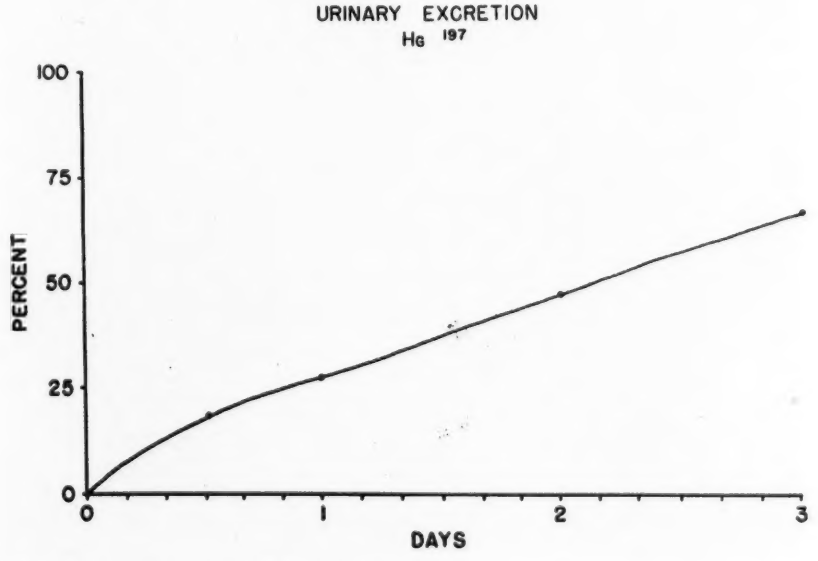

Fig. 3. The urinary excretion of mercury[197].

hours and the 72-hour excretion was 75 per cent of administered dose. The effective half-life was calculated to be 1.16 days. Utilizing *in vivo* counting techniques, the kidney one-half time was approximately 1.16 days. Of extreme interest, 30 per cent of the given dose localized in hepatic and splenic areas. Respective radiation dosages are presented in Table I with comparable radiation dosage of mercury^{203} Neohydrin, both calculated per 100 microcuries of isotope administered.

Organ Photoscanning with Unbound Mercury^{197}:

It is known that ionic mercury attaches to available sulfhydryl groups. The liver and the kidney with their active transport mechanisms have high concentrations of sulfhydryl enzymes. Mercury^{203} Neohydrin^{2} has already been proven as a renal scanning agent, so we were not surprised when we obtained excellent renal scans between one and five hours postintravenous dosage of 100 to 200 microcuries of mercuric^{197} chloride (Fig. 4). However, fifteen minutes after dosage we found excellent concentration of mercuric^{197} chloride, not only in the liver and kidney but also over the splenic bed. Since this discovery, we have had no difficulty in outlining the spleen with this technique which circumvents the tedious heated red blood cell chromium^{51} procedure, giving the spleen one-thirtieth the radiation dose received during the chromium^{51} study (3) (Figs. 5a

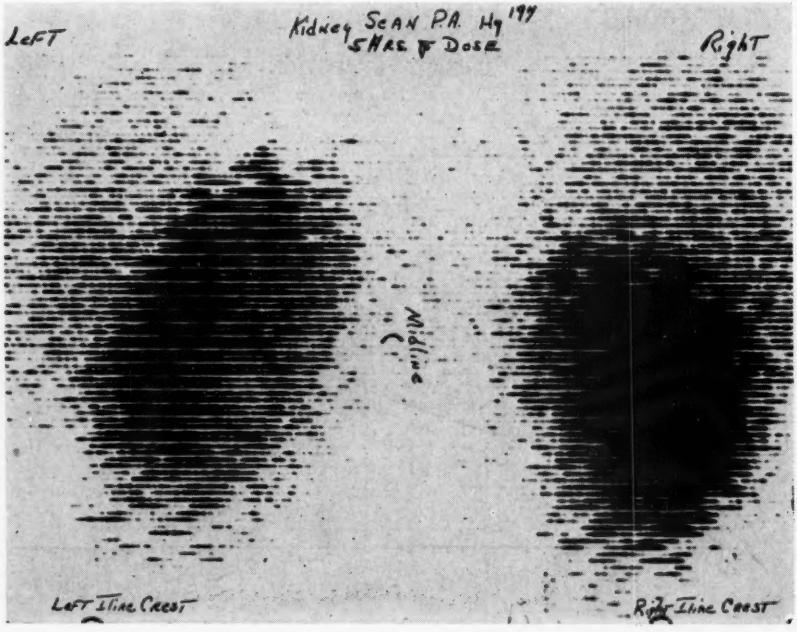

Fig. 4. Normal kidney scan utilizing 150 μc of mercury^{197} done 5 hours post-dose.

& 5b). Mercuric^{197} chloride also gives a reproducible diagnostic liver scan, and as so many of our patients have hepatosplenic diseases we follow our spleen scan with a hepatic scan. Whether mercuric^{197} chloride is as successful as gold^{198} as a liver scanning agent is now under scrutiny (Fig. 6).

Finally, in the evaluation of an intra-abdominal mass, the spleen, liver, and renal scan can be done with the same diagnostic dose of mercury^{197} and superimposed on a flat plate, intravenous pyelogram or other suitable x-ray for proper localization (Figs. 7a & 7b).

In this preliminary evaluation of mercuric^{197} chloride, it has been noted that the unbound isotope is of little use in brain scanning due to its prolonged blood clearance, but we have found 20 to 25 times the concentration of mercury^{197} in brain tumor tissue compared to normal brain tissue 4 to 24 hours after injection. The two brain tumors were astrocytomas.

DISCUSSION

We have recently witnessed a marked increase in interest of isotope scanning due to improved photoscanning devices and better understanding of collimation. Mercury^{203} Neohydrin was introduced by Bender and Blau just two years ago, and now many centers have made brain scanning a practical screening procedure of neurological problems. The renal tubular concentration of mercury has also

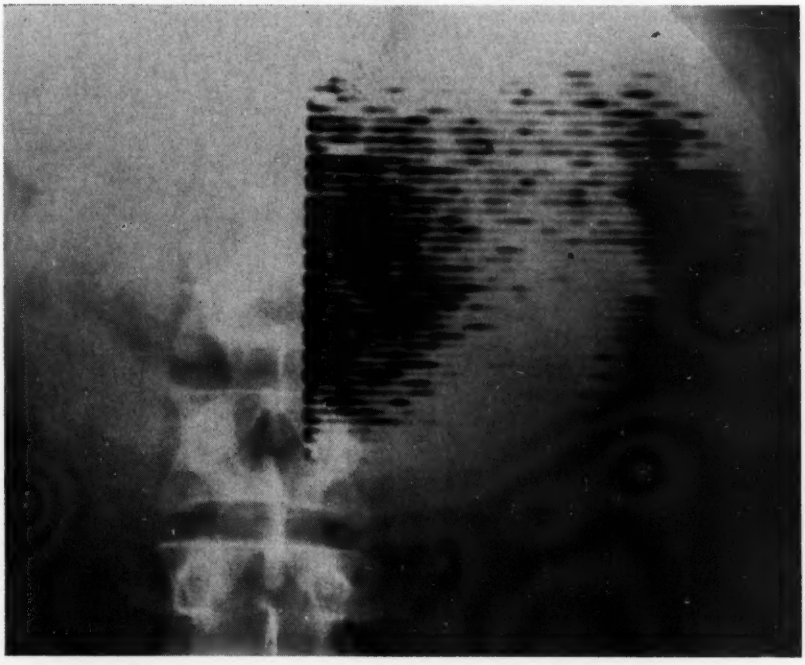

Fig. 5a Scan #1: Spleen scan done 15 minutes after the injection of 150 μc of mercury^{197} revealing a slightly enlarged spleen.

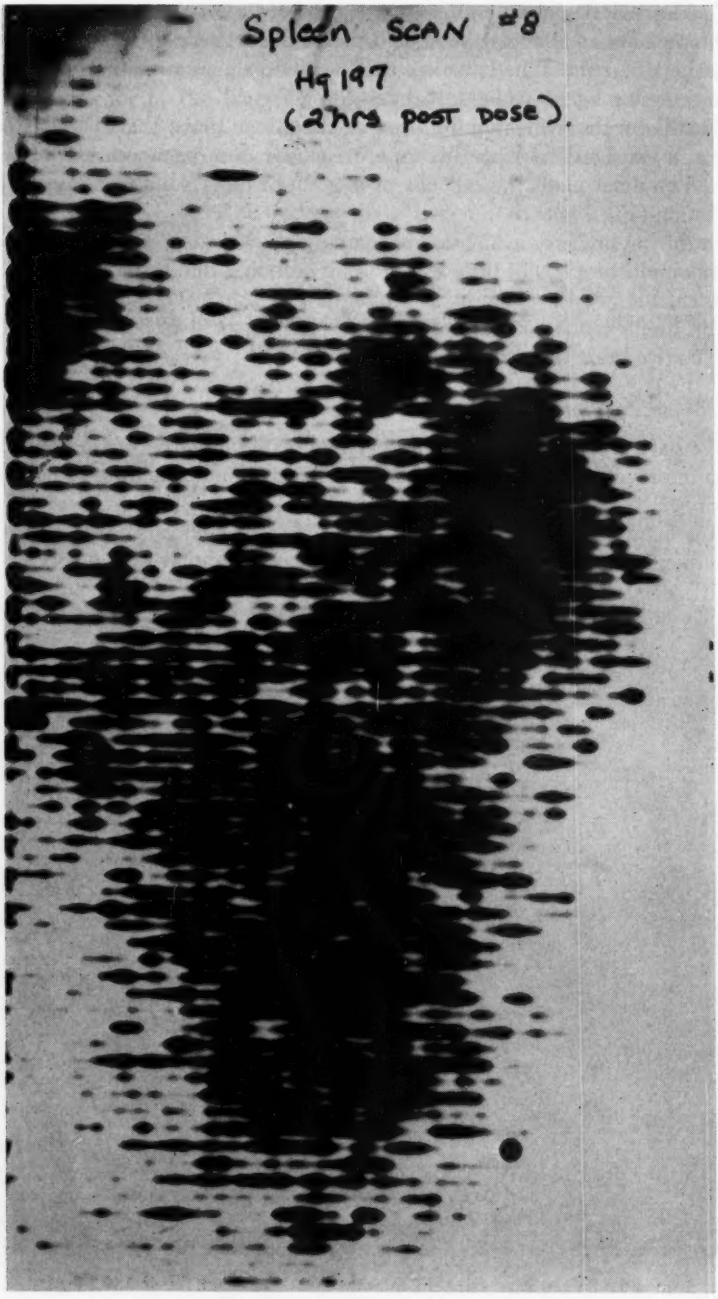

Fig. 5b Scan #2: A grossly enlarged spleen with reticulum cell sarcoma infiltrating the upper pole.

been used to photoscan this organ. However, it has been calculated that the brain scan dose of mercury[203] Neohydrin will give a radiation dose of 45 to 48 rads to the kidneys. This radiation level is acceptable when comparing this dose to other commonly employed radiological diagnostic procedures, but we have attempted to reduce mercury[203] radiation dose by several means. Our efforts included predosing with mercuhydrin and mannitol infusion but no decrease in the amount of mercury[203] in the kidneys could be obtained. Salyrgan mercury[203] was utilized, and although radiation dosage to the kidney was reduced by two-thirds, the blood clearance was so rapid that tumor retention of mercury[203] was decreased.

The evaluation of mercuric[197] chloride was undertaken because of suspected decrease in radiation dosage to the patient due to its short half-life and lack of beta decay. Our study concluded that mercuric[197] chloride and mercuric[203] Neohydrin renal scans are comparable with the former giving one-eighth the radiation dose to the kidneys that the latter delivers. We also found that mercuric[197]

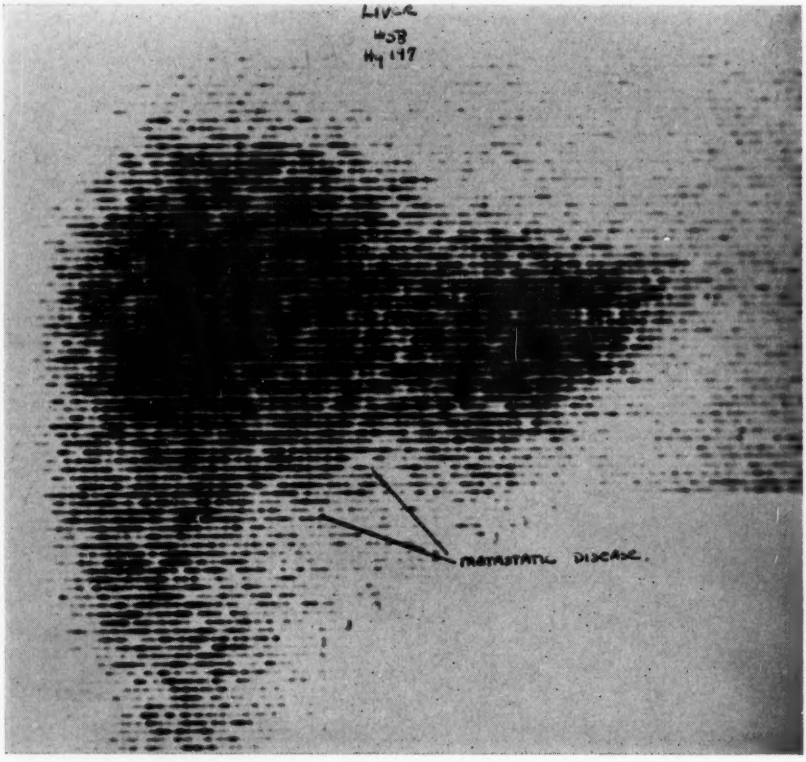

Fig. 6. Liver scan utilizing 200 μc of mercury[197] done at one hour post-dose, revealing known metastatic disease infiltrating the medial border of the right lobe.

chloride localized in the hepatosplenic area to the extent that diagnostic scans were obtained. The mercuric[197] chloride spleen scan was superior to chromium[51] heat-treated red cell scans due to time saved, as well as the decreased radiation dose to the spleen. The accompanying liver scan has been of aid in liver-spleen diagnostic problems. In both of these organs, the mercuric[197] chloride scan is probably due to mercuric[197] chloride sulfhydryl attachments, as our scans in replacement diseases of spleen and liver reveal "cold areas."

This early investigation of mercury[197] introduces a new isotope to clinical medicine. We have shown that the mercuric[197] chloride will give a reproducible diagnostic photoscan of liver, kidneys and spleen with much less radiation exposure than previous isotopes recommended for scans of these organs. It is apparent that a diuretic tagged with mercuric[197] chloride will further reduce radiation exposure to the patient in future brain and other organ photoscanning investigations.

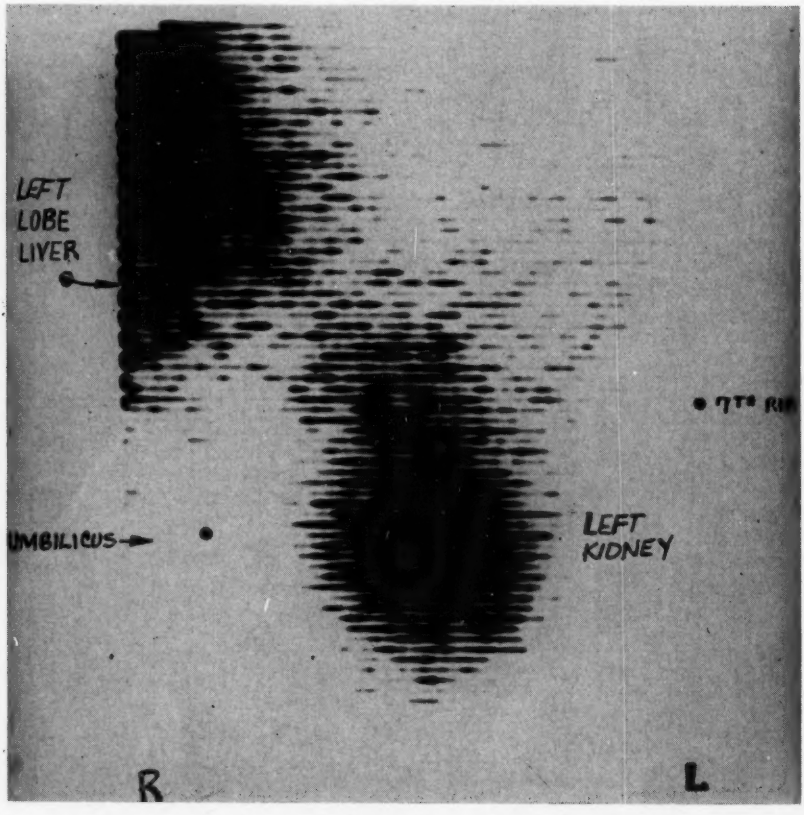

Fig. 7a Liver, spleen and kidney scan utilizing 250 microcuries of mercury[197].
***Scan #1* was done anteriorly and reveals depression of the left kidney and destruction of the spleen.**

ADDENDUM

Following the completion of this manuscript, we evaluated mercury[197] chloromerodrin[1] and obtained renal and brain scans of excellent diagnostic quality. The estimated radiation dosage to the whole body is .0002 rads and to the kidneys .036 rad per 100 microcuries of mercury[197] chloromerodrin.

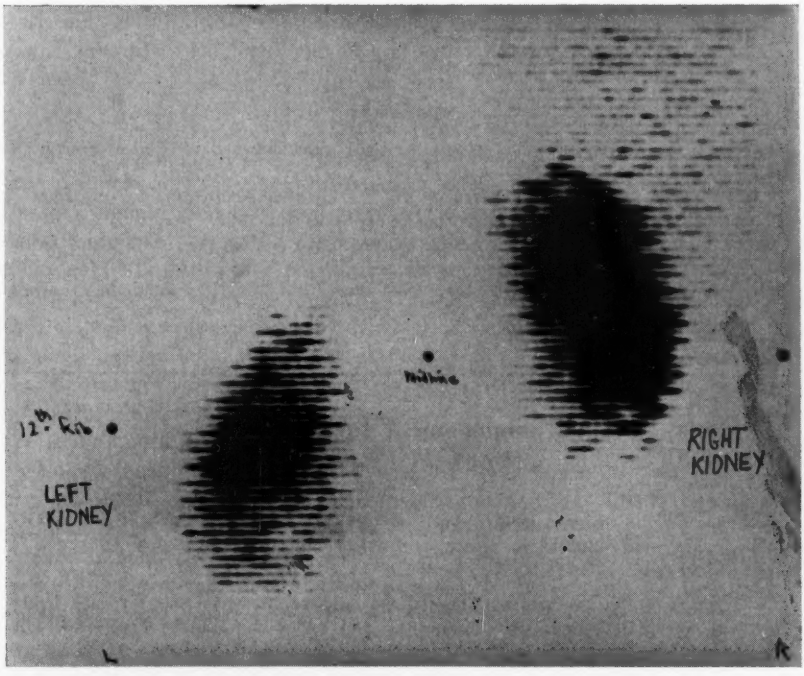

Fig. 7b *Scan* **#2 confirms the kidney position. At surgery, an anaplastic metastic carcinoma was found in the left upper quadrant totally destroying the spleen.**

SUMMARY

1. The human organ localization and excretion of intravenous mercuric[197] chloride was investigated.
2. The radiation exposure to the human kidney was reduced from 5 rads, utilizing mercury[203] Neohydrin to .6 rad with mercury[197] per 100-microcurie dose.
3. Diagnostic photoscans were produced of the kidneys.
4. Diagnostic photoscans were also produced of liver and spleen with far less radiation to the individual organ than with the previously recommended scanning isotope.

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[1]Supplied by Squibb Institute for Medical Research, courtesy of Dr. G. E. Lindenblad.

5. Twenty to twenty-five times more mercury^{197} localized in brain tumor tissue than normal, but slow clearance of blood makes brain scanning impractical with unbound mercury^{197}.
6. Chloromerodrin tagged with mercury^{197} will further reduce radiation dose to the kidney of the patient by a factor of 200.

ACKNOWLEDGMENT

I thank Professor Kellershohn of the Laboratory of Physics, Faculty of Medicine, Paris, France, for the suggestion of mercury^{197} as a scanning isotope.

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Announcement to Authors
Preliminary Notes

Space will be reserved in each issue of THE JOURNAL OF NUCLEAR MEDICINE for the publication of one preliminary note concerning new original work that is an important contribution in Nuclear Medicine.

Selection of the preliminary note shall be on a competitive basis for each issue. One will be selected after careful screening and review by the Editors. Those not selected will be returned immediately to the authors without criticism. Authors may resubmit a rejected or revised preliminary note for consideration for publication in a later issue. The subject material of all rejected manuscripts will be considered confidential.

The text of the manuscript should not exceed 1200 words. Either two illustrations, two tables, or one illustration and one table will be permitted. An additional 400 words of text may be substituted if no tables or illustrations are required. Only the minimum number of references should be cited.

Manuscripts should be mailed to the Editor, Dr. George E. Thoma, St. Louis University Hospital, 1325 South Grand Blvd., St. Louis 4, Missouri. They must be received before the first day of the month preceding the publication month of the next issue, e.g., preliminary notes to be considered for the November, 1963 issue must be in the hands of the Editor before October 1, 1963.

JOURNAL OF NUCLEAR MEDICINE 4:345-358, 1963

Pulmonary Function Test Using Krypton-85[1,2]

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Uneven ventilation of the lung can be demonstrated by the use of inert gas or gas mixtures that do not diffuse through the alveolar capillary membrane. Hydrogen, helium, and nitrogen have been used. Radioactive xenon has been used by Knipping (10) and radioactive oxygen by Dyson (7) in order to correlate clinical findings of obstructive pulmonary lesions with physiological findings.

This study attempts to correlate conventional pulmonary function tests with a pulmonary clearance method using radioactive Krypton. Since the conventionally used pulmonary function studies require much time, skilled personnel, and considerable cooperation of the patient, we have attempted to provide a simpler procedure.

Specific lung diseases show specific patterns of ventilation and lung volume using conventional spirograms: we have attempted to establish similar patterns using radioactive Krypton. Our study uses a multiple breath open circuit method. (Fig. 1)

The radioactivity is determined in a constant flow of exhaled gas through a monitoring device. We use the Dynacon Electrometer (Fig. 2) for this purpose. In this study we are concerned with both lungs as a single respiratory unit.

Physical Data of Krypton-85[6]

Krypton-85 is a gas produced as one of the fission products which result from the slow neutron fission of Uranium-235.
Radiation from Krypton-85 consists of:

Beta particles	0.695 M.E.V. (99%)
	0.150 M.E.V. (0.65%)
Gamma ray	0.540 M.E.V. (0.65%)
Physical half life:	10.27 Years
Biological half life:	less than 3 minutes

[1]Paper Was Presented At The 9th Annual Meeting of Society of Nuclear Medicine, June 28, Dallas, Texas.
[2]Cook County Hospital.
[3]Research Associate.
[4]Chief of Thoracic Surgery.
[5]Physicist.
[6]Krypton-85 can be obtained from Oak Ridge National Laboratory, Oak Ridge, Tennessee.

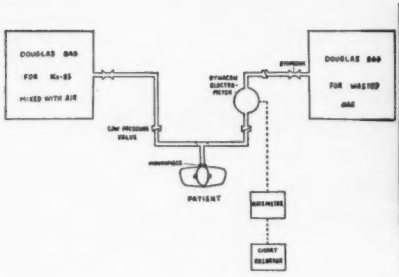

Figure 1

Schematic diagram of Kr-85 Pulmonary Function Test.

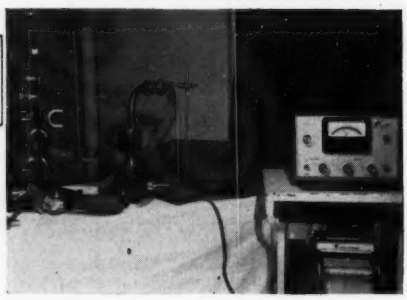

Figure 2

Dynacon Electrometer & Recording Equipment.

Krypton-85 is an inert gas and is rapidly and completely excreted from the body through the lungs. Due to the short Biological half life the long physical half life does not cause a radiation hazard to the patient. Its long physical half life permits storage of the gas almost indefinitely.

PROCEDURE

1. The patient breathes a controlled air mixture containing 0.05-0.1 microcurie of radioactive Krypton per milliliter of air. The respiratory exchange of air and the Krypton-85 air mixture is monitored for radioactivity until an equilibrium state is reached. This is indicated by a flattening of the curve which indicates activity of exhaled gas plotted against time. This state is usually reached in 2 minutes: however, in order to be entirely sure that an equilibrium state exists breathing is usually continued for 5-6 minutes. (Fig. 3) The expired air is monitored in a continous gas flow counter until its Krypton-85 content is essentially zero. The Krypton-85 activity in expired air is shown graphically on a chart recorder.

Referring to Figure 4B, the extremely steep slope to the right of the plateau represents primarily the wash out of radioactivity from the anatomical dead space. When the activity has reached approximately 1/100 of its original value, the patient is asked to perform a series of vital capacities approximately one minute apart. As a result of vital capacities performed at this activity level, the peaks occurring in the curve indicate forced removal of released air from alveolar or equivalent space such as a cyst. Due to operating characteristics of the rate meter-chart recorder used, peaks are cut off at a value of 10^2, which will be called a 100 per cent peak. This in no way invalidates the data in which we are interested. The area concerned in diagnostic evaluation lies in the area represented by activity of 1/100 or less of the original activity.

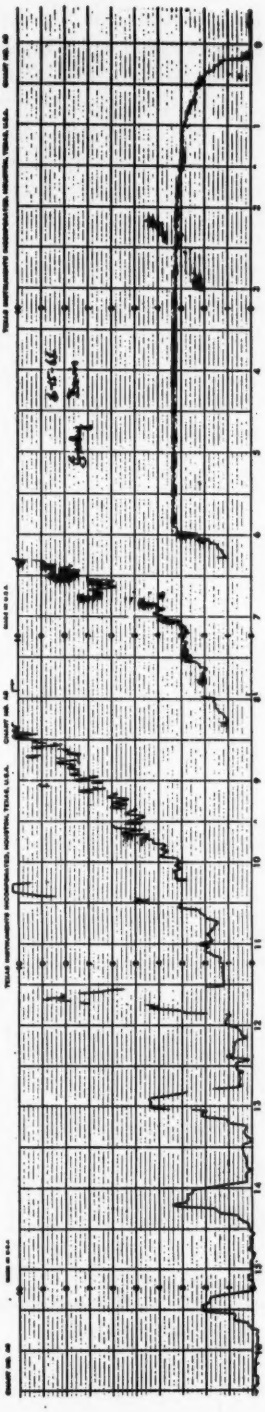

Figure 3. An example of original chart recording of a case of minor pulmonary emphysema.

2. After equilibrium has been reached the radioactive Krypton air mixture supply is abruptly stopped and routine air respiration is restored.

We have tried to establish basic patterns of breathing by breath recordings of the radioactive Krypton clearance for normal lungs and for lung diseases presenting restrictive or obstructive ventilatory defects.

We have also tried to establish similar basic patterns for gross intrapulmonary or extra-pulmonary diseases presenting restrictive patterns in conventional spirograms. Additionally we have determined the presence of cystic diseases of the lung whether or not the cysts communicate with the bronchial tree.

ILLUSTRATIVE CLINICAL APPLICATION

Case I.

G.A. A 34 year old white female who is in perfect health. X-ray shows normal chart (Fig. 4A).

Conventional pulmonary function studies are:

Vital capacity	4270cc (130% of predicted)
Residual volume	1870cc
Functional Residual capacity	3660cc
Total lung capacity	6070cc (149% of predicted)
RV/TLC X 100	30%
Timed vital capacity (1 Sec.)	70%
Intra-pulmonary mixing index	1.3% N_2 1.25% N_2

DIAGNOSIS

Within normal.

Krypton-85 clearance time is 4.5 minutes (ref. chart I) and there is no 100 per cent high peak by vital capacity performance. (Fig. 4B)

Figure 4A

Case I. Normal chest radiograph.

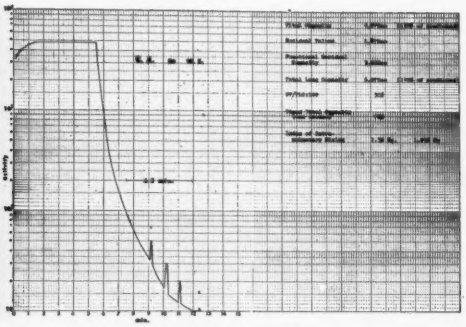

Figure 4B

Kr-85 Pulmonary clearance in a normal case. (Case 1)

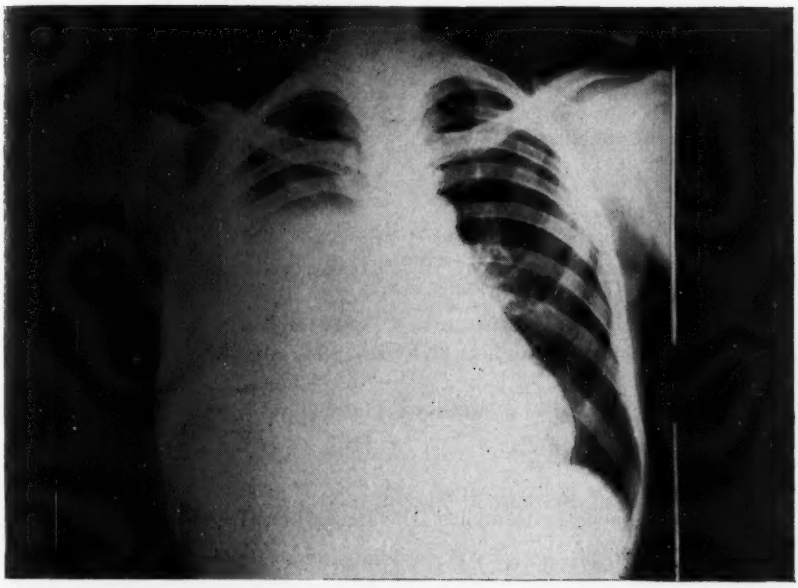

Figure 5A

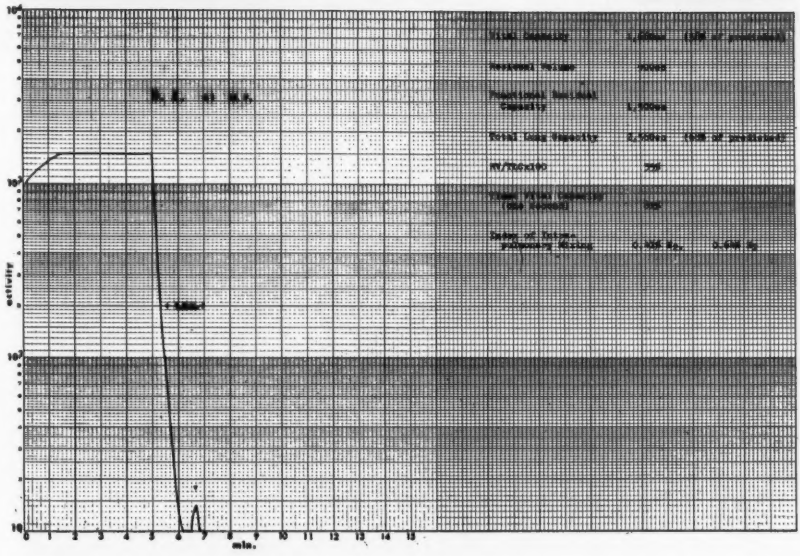

Figure 5B

Figure 5A. Chest radiography showing massive pleural effusion occupying right lower 2/3 of thoracic cavity (Case 2)

Figure 5B. Kr-85 Pulmonary clearance where there is marked restrictive ventilatory defect due to massive pleural effusion (Case 2)

Case II.

D.A. A 41 year old negro female who was admitted to the hospital following stab wound which produced massive right hemothorax. X-ray shows massive pleural effusion in right hemithorax. (Fig. 5A)

Conventional pulmonary function studies show:

Vital capacity	1,660 cc (58% of predicted)
Residual Volume	900cc
Functional residual capacity	1,500cc
Total lung capacity	2,560cc (68% of predicted)
RV/TLC X 100	35%
Timed vital capacity (1 sec.)	81%
Intra-pulmonary mixing index	0.41% N_2 0.84% N_2

DIAGNOSIS

Severe restrictive ventilatory defect.

Krypton-85 clearance time is 1.5 minutes (ref. Chart I) and the maximum peak is very low by vital capacity performance. This indicates restriction in comparison with normal case. (Fig. 5B)

Case III.

M.S. A 25 year old negro male who presented a history of shortness of breath for the last 2 years. X-ray shows a diffuse pulmonary fibrosis and bilateral pleural adhesion. (Fig. 6A)

Conventional pulmonary function studies show:

Vital capacity	2,700cc (63% of predicted)
Residual Volume	325cc
Functional Residual Capacity	2,000cc
Total lung capacity	3,030cc (57% of predicted)
RV/TLC X 100	11%
Timed Vital Capacity (1 sec.)	77%
Index of Intra-pulmonary mixing	0.72% N_2 1.07% N_2

DIAGNOSIS

Restrictive ventilatory defect.

Krypton-85 clearance time is 3 minutes (ref. Chart I) and there is no 100% peak of vital capactiy performance. (Fig. 6B) In comparison with a normal case pattern, this case shows a restrictive pattern.

Case IV.

V.M. A 54 year old white male with a 12 year history of progressive shortness of breath and a recent episode of cardiac decompensation. X-ray shows

marked pulmonary emphysema. (Fig. 7A)
Conventional pulmonary function studies show:

Vital Capacity	1,930cc (52% of predicted)
Residual Volume	3,300cc
Functional Residual Capacity	4,360cc
Total Lung Capacity	5,240cc (98% of predicted)
RV/TLC X 100	63%
Timed Vital Capacity (1 sec.)	39%
Index of Intra-pulmonary Mixing	12.55% N_2 8.13% N_2

DIAGNOSIS

Severe obstructive ventilatory defect with moderate restriction. Krypton-85 clearance time is 12.5 minutes (ref. Chart I) and there are two 100 per cent peaks by vital capacity performance.
This case shows severe emphysema in comparison with normal case.

Case V.

J.D. A 50 year old negro male who presented left anterior chest pain and a 5 year progressive shortening of breath, especially during exertion. X-ray showed a large emphysematous bleb occupying two-thirds of the left lower lung field and emphysematous changes in the right lung. (Fig. 8A) Bronchogram revealed tubular bronchiectasis of all basal segments which are compressed by the cyst. There is no evidence of bronchial connection with cyst. (Fig. 8B, 8C)
Conventional pulmonary function studies show:

Vital Capacity	2,000cc (51% of predicted)
Residual Volume	1,850cc
Functional Residual Capacity	3,120cc
Total Lung Capacity	3,950cc (70% of predicted)
RV/TLC X 100	4%
Timed Vital Capacity (1 sec.)	48%
Index of Intra-pulmonary Mixing	6.86% N_2 5.40% N_2

CHART I

"DIAGNOSIS OBTAINABLE FROM RADIOACTIVE GAS METHOD"

	Clearance Time	*100% Peak*
Normal	3 - 6 minutes	0 - 1
Restrictive Ventilatory Defect	Less than 3 min.	None
Emphysema, minor	6 - 9 minutes	1 - 2
Emphysema, moderate	9 - 12 minutes	1 - 3
Emphysema, severe	More than 12 min.	2 - 4
Cyst $\bar{S}$ bronchial connection	Same as minor to moderate emphysema. X-ray correlation is necessary	
Cyst $\bar{C}$ bronchial connection	More than 12 min.	More than 4

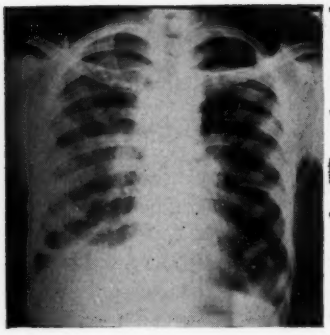

Figure 6A

Case 3. Chest radiography showing diffuse pulmonary fibrosis and bilateral pleural adhesion.

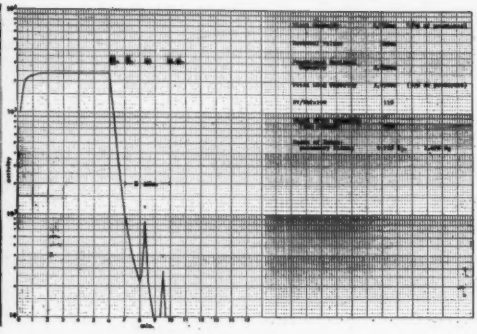

Figure 6B

Kr-85 pulmonary clearance where there is restrictive ventilatory defect due to diffuse pulmonary fibrosis. (Case 3).

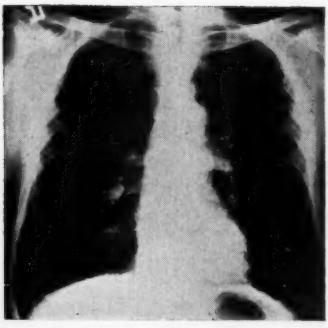

Figure 7A

Case 4. Chest radiography showing marked pulmonary emphysema.

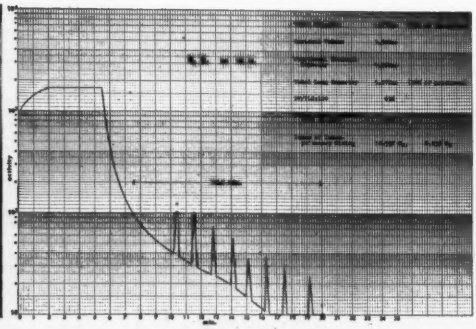

Figure 7B

Kr-85 pulmonary clearance for Case 4

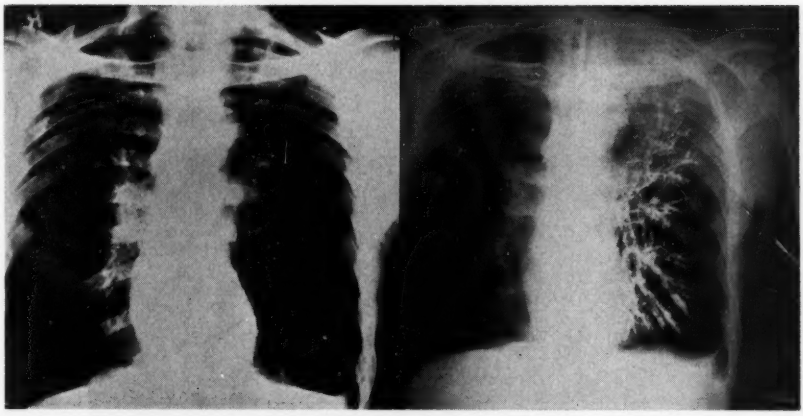

Figure 8A

Case 5. Chest radiography showing large cyst in lower lung field and emphysema in both lungs.

Figure 8B

Case 5. Bronchogram showing medially compressed bronchial trees by the cyst and tubular bronchiectasis.

DIAGNOSIS

Obstructive ventilatory defect with marked restriction. Krypton-85 clearance time is 7.5 minutes (ref. Chart I) and there is only one 100 per cent peak by vital capacity performance. (Fig. 8D) This finding indicates only minor degree of pulmonary emphysema. With correlation of plain chest (P-A view) X-ray, this

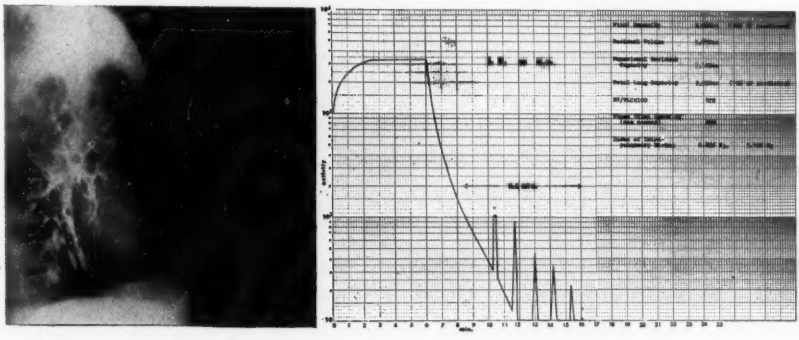

Figure 8C

Case 5. Lateral view of bronchogram shows posteriorly compresses bronchial trees by the cyst, which indicates no bronchial connection with cyst.

Figure 8D

Kr-85 pulmonary clearance where there is lung cyst without bronchial connection (Case 5)

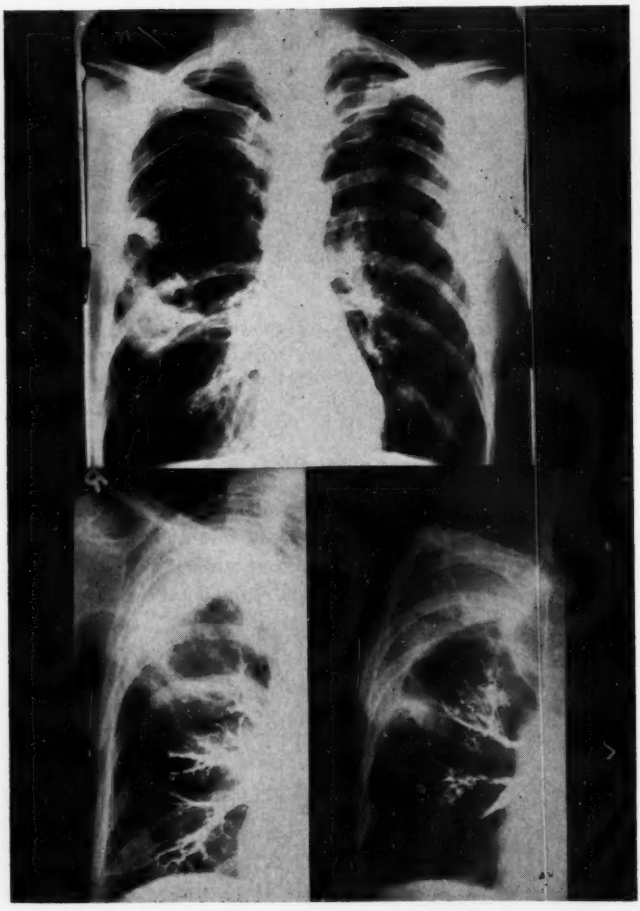

Figure 9A

Figure 9B

Figure 9A. Case 6. Chest radiography showing a large cyst in the right upper lung field compressing the lung parenchyma. Left lung shows emphysema.

Figure 9B. Case 6. Bronchogram of Case 6, shows contrast media spillage into the cyst, which indicates that the cyst is connected with the bronchial trees.

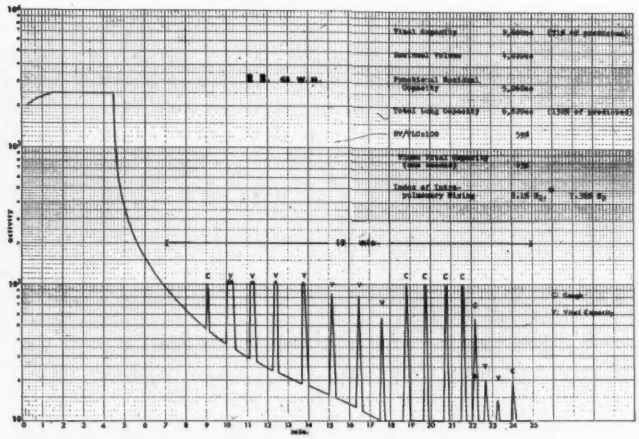

Figure 9C. Kr-85 Pulmonary clearance for Case 6.

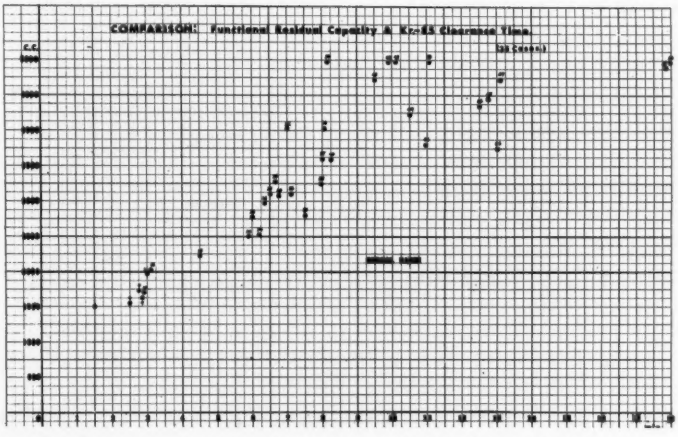

Figure 10. Comparison between Kr-85 pulmonary clearance time and functional residual capacity of lung in individual cases.

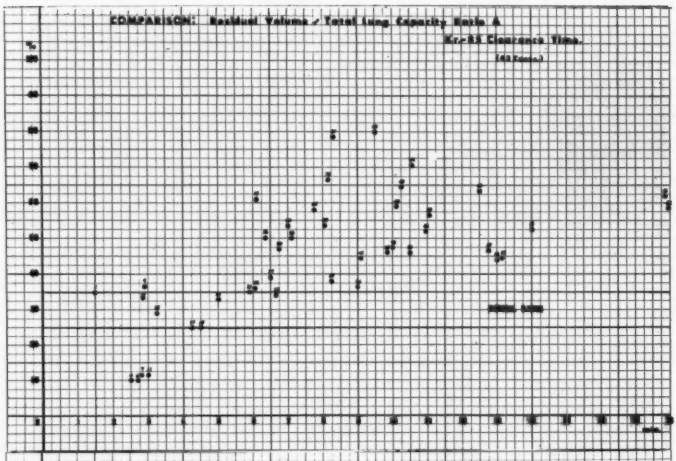

Figure 11

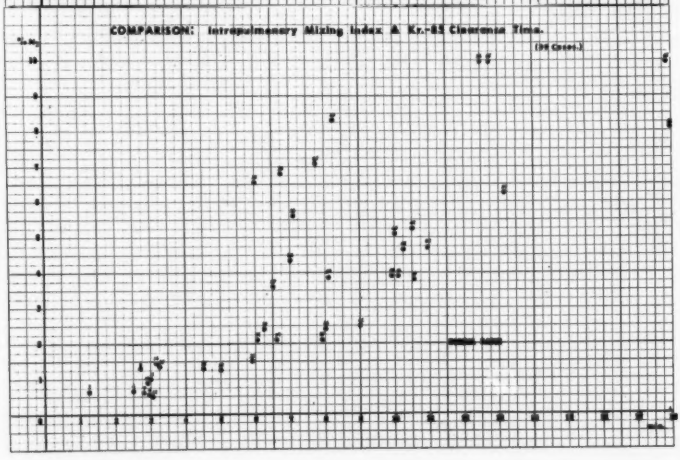

Figure 12

Figure 11. Comparison between Kr-85 pulmonary clearance time and radio of residual volume to total lung capacity in individual cases.

Figure 12. Comparison between Kr-85 pulmonary clearance time and intra-pulmonary mixing index in individual cases.

finding indicates that the cyst is not connected with bronchial tree, which was proved by bronchogram study (Fig. 8B, 8C).

Case VI.

R.B. A 48 year old white male who presented a history of progressive shortness of breath during the last 2.5 years and frequent episodes of right lung pneumonitis. Chest x-ray shows a large pulmonary cyst occupying upper one-half of right hemithorax which compresses the lung parenchyma. The left lung shows emphysema. (Fig. 9A)

Pulmonary function studies show:

Vital Capacity	2,800cc (71% of predicted)
Residual Volume	4,020cc
Functional Residual Capacity	5,060cc
Total Lung Capacity	6,820cc (132% of predicted)
RV/TLC X 100	59%
Timed Vital Capacity (1 sec.)	43%
Index of Intra-pulmonary Mixing	8.1% N_2 7.36% N_2

DIAGNOSIS

Severe obstructive ventilatory defect with mild restrictive component.
Krypton-85 clearance time is more than 18 minutes (ref. Chart I) and there are eight 100 per cent peaks by vital capacity performance and coughs. (Fig. 9C) In comparison with Case 5 and the rest of the cases, this finding indicates the cyst is connected with bronchial tree. Bronchogram shows that the contrast media spills into the cyst, which proves that the cyst is connected with the bronchial tree.

DISCUSSION AND SUMMARY

The measurement of the breath by breath Krypton-85 clearance depends upon the volume of the gas mixture in the alveoli, the Functional residual volume, respiratory rate, and size of dead space. Therefore, we compared the Krypton-85 clearance time with functional residual volume (Fig. 10) and the ratio of residual volume to total lung capacity (Fig. 11). Since the study has its background in the nitrogen wash out method with end alveolar sample nitrogen content, we also made comparisons with the intra-pulmonary mixing index (Fig. 12).

These comparison charts indicate that the conventional pulmonary function studies and Krypton-85 clearance time are consistent with each other.

Approximately 100 cases of various pulmonary diseases have been studied to date and 62 of these cases were compared with conventional pulmonary function tests.

With this test, we were able to differentiate between normal and abnormal pulmonary function. Furthermore, we were able to differentiate between obstructive and restrictive ventilatory defects, cystic changes in the lung with or without bronchial communication and various types of pulmonary emphysema.

General classification of radioactive Krypton clearance time in various pulmonary diseases are as shown in Chart I.

The advantages of using radioactive gas, Krypton-85, for pulmonary function tests are:

1. Far less time consuming (15-30 minutes per case) than conventional methods.
2. Equally as accurate as conventional methods.
3. Less cooperation required on the part of the patient.
4. Technique is simple.
5. Equipment cost not excessive.
6. Radiation hazard to patient is negligible. Calculations have indicated that the absorbed dose in the lung is approximately the same as would be received when a single P.A. 14 x 17 chest film is taken.

CONCLUSION

Our preliminary investigation using radioactive gas for pulmonary function test reveals promise in simplified pulmonary function studies, particularly for mass screening test.

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JOURNAL OF NUCLEAR MEDICINE 4:359-370, 1963

The Thyroxin-Protein Dissociation Index, A Modified T_3 Resin Uptake Procedure[1,2]

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INTRODUCTION

Thyroxin (T_4) in plasma participates in binding equilibria with at least three protein fractions, thyroid binding globulin (TBG), thyroid binding prealbumin (TBPA), and albumin (1). The availability of thyroxin to peripheral tissues seems to be a function of the amount of thyroxin that exists in the "free state" which is determined by the degree of dissociation of the thyroxin-protein complexes. The extent of this dissociation is a function of the binding affinity of these proteins, their abundance, and the amount of thyroxin present (2).

An index of the net degree of dissociation of thyroid hormone-plasma protein complexes can be obtained by incubating plasma with red cells or ion exchange resin and measuring the per cent of added I^{131} labeled hormone which remains bound to serum after a given period of time. Hamolsky devised a clinically useful test that employs erythrocytes to measure this index (3). This test, the erythrocyte uptake of triiodothyronine (T_3), is performed by adding a trace of I^{131}-T_3 to unclotted whole blood and incubating the mixture. The plasma is removed by washing the erythrocytes, and the per cent of radioactivity remaining on the cells is measured.

Because of technical difficulties with the erythrocyte method, Mitchell introduced the use of resin as a substitute for erythrocytes in the measurement of this index of thyroid function (4). A variety of alterations of Mitchell's original technique have since been proposed (5-10). Despite these changes none of the methods has significantly improved the accuracy of the test nor defined the causes of sporadic fluctuations in results. Most investigators have corrected for these unexplained variations by expressing their results in terms of a control pooled serum. Nevertheless, the presence of unknown factors which are responsible for variations is undesirable. Our investigations were oriented toward the development of a test that is founded on a thorough study of those factors that may affect its accuracy and its reproducibility.

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[1]Supported in part by the National Cancer Institute Research Training Grant CRT-5062.

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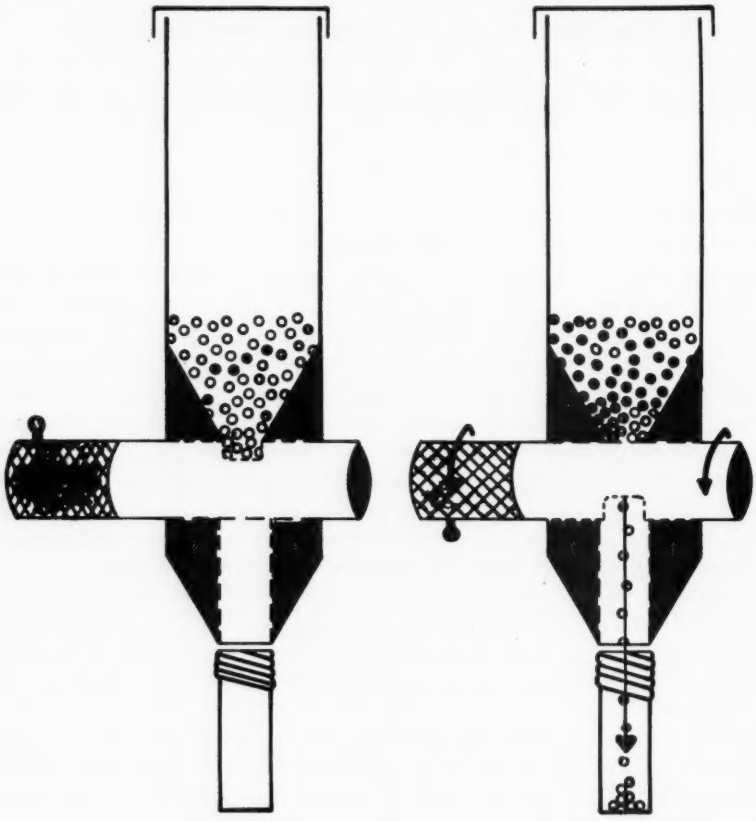
An analysis of earlier publications, together with our observations from preliminary experiments, focused our attention on the need for devising an accurate method for measuring and dispensing resin. A number of experiments were conducted to explore the possibility of using dry rather than wet resin. An acceptable solution to these problems was found. Subsequently, over 4000 tests were



METHOD OF DISPENSING DRY RESIN FROM A GUN POWDER DISPENSING TOOL.

Fig. 1. Method of dispensing dry resin from a gun powder dispensing tool.

performed over an 18 month period on large volumes of pooled serum. Experiments were performed to establish causes of variations and appropriate modifications were introduced.

The method that has evolved and the results of those experiments that illustrate the factors influencing this method are described.

MATERIALS AND METHODS

The I^{131}-T_3 secured from commercial suppliers[1] was stored undiluted at 4°C. A portion of the stock I^{131}-T_3 was diluted with tris-maleate buffer[2] (pH 7.4, 0.2 M) so that the dilution would contain approximately 0.5 uc/ml.

Large volumes of serum pooled from normal volunteers and from laboratory discards were frozen and stored in 15-20 ml aliquots. A standard pooled serum was collected from a large number of normal individuals. This serum was frozen in small lots and used to standardize other large pools of serum to be used as daily controls. Each pool of control serum was assigned a factor (Factor A) which is the ratio of the T_3 uptake of standard serum to the T_3 uptake of control serum.

Amberlite IRA 400, Cl. form, 20-50 mesh ion exchange resin was dried at room temperature for 24 hours. The dried resin was passed through U.S. sieves of 30 and 40 mesh. All resin beads with mesh sizes greater than 40 (smaller particles) or less than 30 (larger particles) were discarded. The sifted resin was stored at room temperature in a sealed container.

A gun powder dispensing tool (Fig. 1) was adapted for use by drilling a well of the appropriate size in the cylinder. The amount of resin delivered by the tool is determined by the size of this well. A constant amount of resin could be dispensed by turning the cylinder of the tool 180°.

One hundred and twenty milligram portions of the prepared resin are dispensed into 4 ml glass screw cap vials. To each vial is added 2 ml of tris-maleate buffer and a glass bead. The vials are made up in large quantities and stored at 4°C.

A 2-ml portion of serum and one drop of T_3 solution, dispensed from a disposable Pasteur pipette, are added to the previously prepared vials. The vials are capped, mixed thoroughly and the amount of radioactivity present in each is determined (initial count). The vials are placed in a temperature controlled water bath[3] and shaken at 230 cycles per minute (half-inch excursions) for two hours in a horizontal position at 38°C. At the end of the incubation the vials are removed and five minutes are allowed for the resin to settle. A 2-ml aliquot of the supernate from each vial is transferred to another vial and diluted to 4 ml with water or saline. The vials containing the aliquots are mixed thoroughly and the radioactivity is measured (final count). Both counts (initial and final) are corrected for background. The serum T_3 uptake value is calculated as follows:

$$\% \text{ Uptake by Serum} = \frac{\text{Final count} \times 2}{\text{Initial count}} \times 100$$

[1]Abbott Laboratories and Nuclear Chicago
[2]Tris-hydroxyaminomethane maleate
[3]Research Specialties Co. Model 2156

The per cent T_3 uptake of control serum is determined. This is adjusted to the standard serum by multiplying by Factor A. The thyroxin-protein dissociation index is calculated as follows:

$$\text{TDPI} = \frac{\%\ T_3 \text{ Uptake of Patient Serum}}{\%\ T_3 \text{ Uptake of Control Serum X Factor A}} \times 50$$

It is to be noted that the ratio of T_3 uptake by patient serum to T_3 uptake by standard serum has been multiplied by an arbitrary constant of 50.

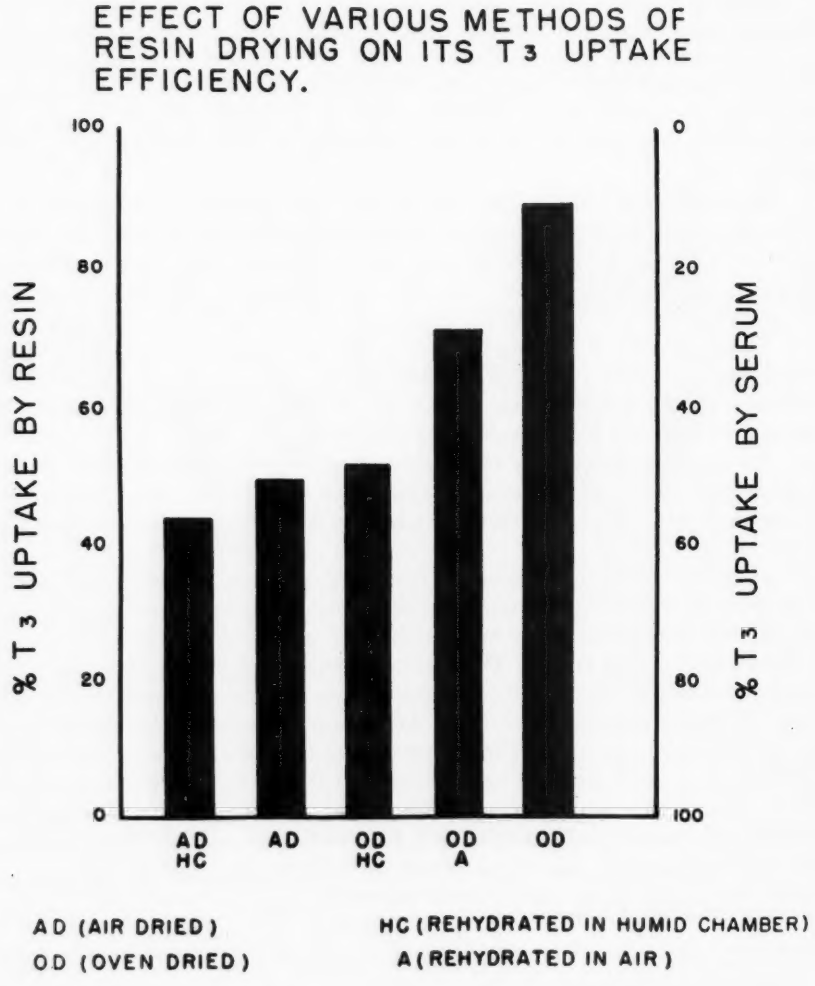


Fig. 2. Effect of various methods of resin drying on its T_3 uptake efficiency.

RESULTS

The average standard deviation of large groups of resin portions dispensed by the gun powder tool was consistently less than 1.0 mg. The average weight of resin portions in each group was generally near 120 mg. Small fluctuations in average weight of the groups was due to slight differences in moisture content from day to day. Resin that had not been dried adequately could not be dispensed accurately since it tended to adhere to the wall of the dispensing tool. Finer grades of resin such as Amberlite CG 400 also could not be dispensed accurately by this method.

Various methods of drying the resin were investigated. These included air drying, oven drying at 50°C., 75°C., and 110°C., and drying in a vacuum desiccator. Desiccation and oven-drying resulted in visible shattering of resin beads upon rehydration of the resin with saline, tris-maleate buffer or serum. This phenomenon was also observed occasionally after prolonged air drying. Fine amorphous resin particles could be seen floating in the supernate within the vials. When shattering occurred accuracy and reproducibility were markedly reduced and the uptake by the resin was increased. Resin which had been air dried for 24 hours and then stored at 22-25°C. for weeks in sealed containers did not shatter when rehydrated. The shattering and the T_3 uptake efficiency of previously desiccated or oven dried resin could be reduced by gradual rehydration in a humid chamber. The magnitude of the effect of these factors on the resin uptake is illustrated in Figure 2.

Air dried resin was screened into three mesh sizes, 20-30, 30-40, and 40-50. T_3 serum uptakes were performed on pooled serum using each of the three groups of resins. The uptake values were dependent on resin size. Thirty-five per cent more T_3 was bound to 120 mg of the 40-50 mesh resin than to a similar weight of 20-30 mesh resin.

An analysis of large numbers of T_3 uptakes of pooled serums performed over a period of several months clearly demonstrated that T_3 uptake values fluctuated with each shipment of T_3. The daily average uptake of multiple determinations on pooled serum using air-dried resin did not vary by more than one per cent when the T_3 used came from the same shipment. The average uptake value of pooled serum varied by as much as 15 per cent when different shipments of T_3 were used. When the average uptake of pooled serum using each of 14 T_3 shipments was compared to the per cent of T_4 present in each specimen (determined by chromatographic analysis), a relationship seemed to exist. A fresh, labeled T_3 sample was seeded with increasing amounts of I^{131}-T_4. The results (Figure 3) indicated that as the per cent of T^4 present in the labeled sample increased, the per cent of radioactivity bound by serum also increased.

A similar experiment was performed to evaluate the role of free I^{131} as a contaminant in T_3 preparation (Fig. 3). One hundred per cent of the added I^{131} became bound to resin. This did not effect the distribution of labeled T_3 but the calculated uptake value was lowered. It was possible to correct the uptake results to the control value with precision by subtracting the activity added as free I^{131} from the initial count.

Labeled T_3 lots gave stable results over a period of at least two weeks and occasionally for as long as one month. When T_3 stored longer than two to four weeks was used the T_3 uptake values fluctuated erratically.

Wide variations in the amount of T_3 added to test vials did not affect the uptake results. For this reason it was permissible to dispense the T_3 solutions as a single drop via a Pasteur pipette.

Serum was preferable to plasma since fibrinogen caused clumping of the resin. Large amounts of hemolysis had no effect on the T_3 uptake. Added hemoglobin in concentrations far exceeding those usually seen in clinical serum samples had no detectable effect on the uptake values. Serum stored at 4°C. was stable for at least four weeks and probably much longer. Nonrefrigerated serum was stable for at least one week. Blood specimens refrigerated without separating serum

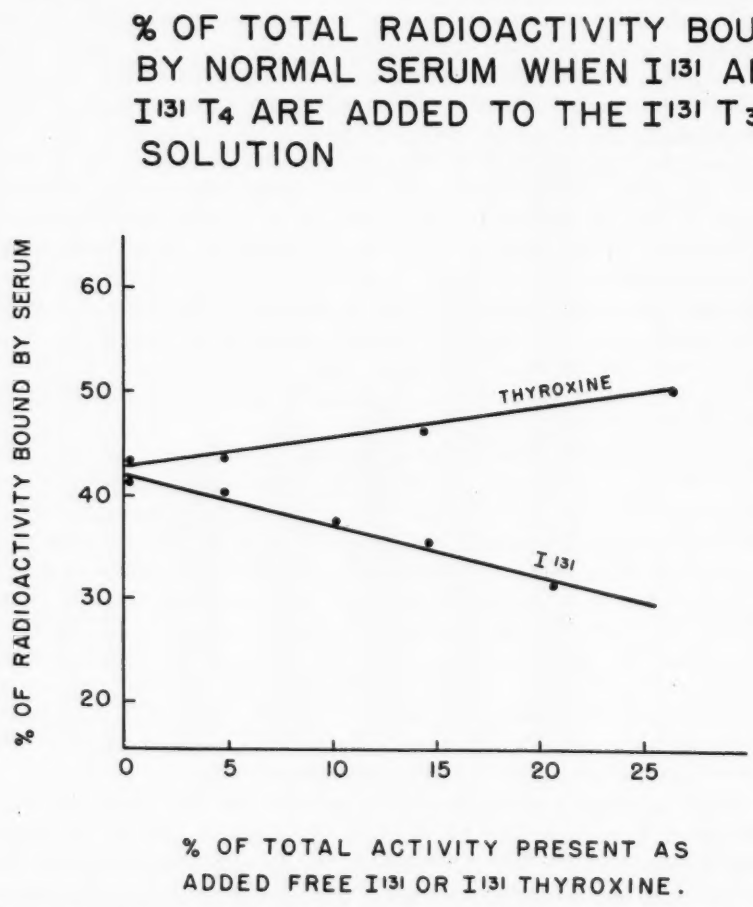


Fig. 3. Percentage of total radioactivity bound by normal serum when I^{131} and $I^{131}T_4$ are added to the $I^{131}T_3$ solution.

from the clot did not result in changes in uptake activity of the serum during a four week period.

Figure 4 illustrates the effect of temperature of incubation and duration of incubation on the T_3 uptake by serum. By two hours the curve approaches a plateau. The level of the plateau at two hours is dependent on the temperature of incubation. Higher temperatures result in lower T_3 uptakes by serum.

T_3 uptakes were performed on pooled serum at shaking rates varying from 50 to 250 half-inch excursions per minute. The most consistent results were obtained at shaking rates greater than 200 per minute. At slow shaking rates the uptake by the resin was lower. The position of vials during incubation effects the uptake volume by modifying the degree of agitation of resin. For this reason a rack was constructed so that the vials could be kept in a uniform horizontal position during incubation.

Prior incubation (38°C.) of T_3 with serum did not effect the T_3 uptake value. Similarly, a delay of thirty minutes between the addition of T_3 to the serum-resin mixture and the onset of incubation caused no significant change in the serum T_3 uptake after two hours of incubation. When the test vials were removed from the incubator shaker and allowed to stand at room temperature for up to 30 minutes, no differences in T_3 uptake values could be demonstrated.

The "spread" between the T_3 uptake of standard and pooled pregnancy sera was compared under a variety of conditions. The per cent uptake of normal pooled serum was made to vary progressively from 10 to 80 per cent by varying temperature or the amount of serum or the amount of resin. Under these conditions, the maximum spread between standard and pregnancy serum was obtained when uptakes of standard serum was between 35 and 40 per cent. When the test conditions were altered by varying the pH of the tris-maleate buffer, the

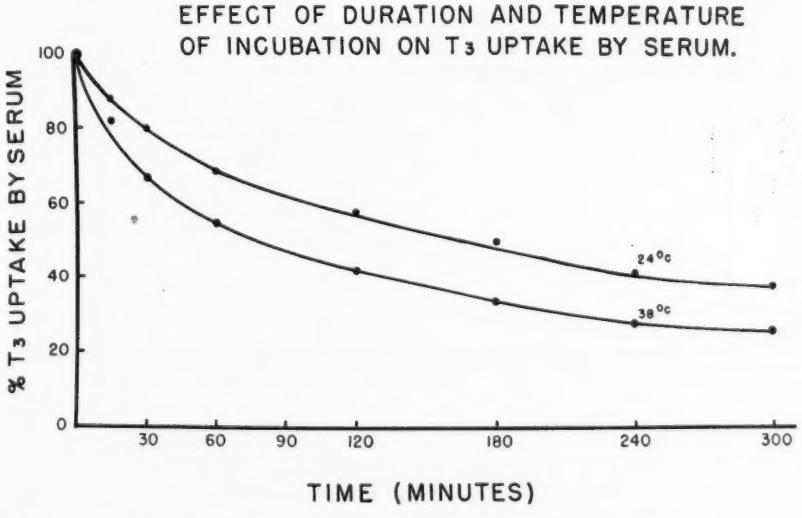


Fig. 4. Effect of duration and temperature of incubation on T_3 uptake by serum.

maximum spread again occurred when uptake values of standard pooled serum were near 35-40 per cent (Fig. 5).

As the T_3 uptake values of pooled normal serum approached 0 or 100 per cent the T_3 uptake values of pooled normal and abnormal serums approached the same values and the differences of T_3 uptake among them decreased. Under conditions which resulted in T_3 uptakes by normal serum approaching zero per cent, small differences in resin mass caused large changes in per cent serum uptake (Fig. 6).

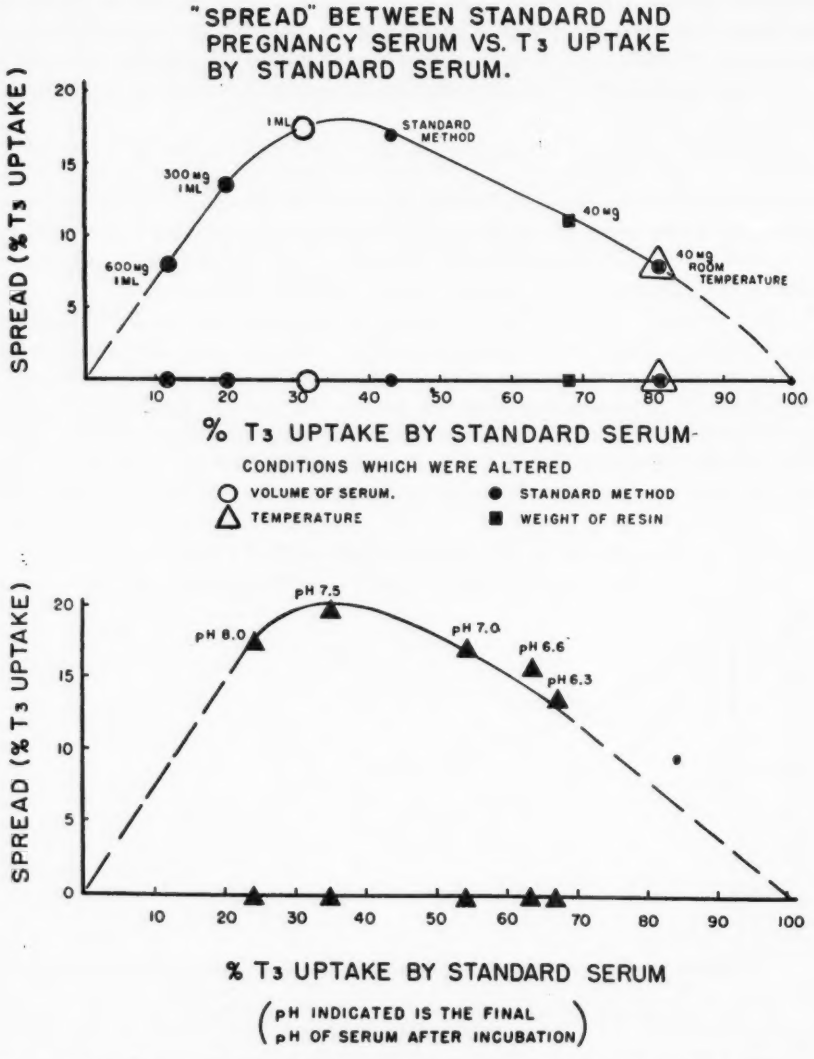


Fig. 5. "Spread" between standard and pregnancy serum vs. T_3 uptake by standard serum.

The majority of these experiments were conducted using 2 ml of serum in vials containing resin and 2 ml of tris buffer. When 1 ml of serum and 3 ml of tris were substituted, the value of the serum uptake was reduced. However, when the amount of resin used was concomitantly reduced, the uptake values could be returned to the desired values and the sensitivity of the measurement could be retained.

A number of experiments were conducted using a tube rotator at room temperature in place of the incubator shaker. To compensate for the lower resin efficiency at room temperatures more resin was used. This procedure compared favorably to our standard method.

The reproducibility of this test was determined from an analysis of 300 T_3 uptakes performed on pooled serum over a four month period. Eleven separate T_3 specimens were used during this period. Only those tests that were performed within two weeks from the date of assay of the T_3 specimens are included. The resin originated from a single source, but dispensing was accomplished on four different days. The daily averages varied from a low of 55.4 per cent to a high of 60.0 percent. The average of 61 groups was 57.9 per cent and the S.D. was 1.3 per cent. The S.D. of groups of tests performed on each T_3 specimen varied from 0.2 per cent to 1.1 per cent with an average S.D. of 0.7 per cent. The average S.D. of individual groups from the mean of all groups employing the same T_3 was 0.7 per cent. A group of 60 tests were performed on a single day. The average of this group was 49.6 per cent with a S.D. of 0.9 per cent.

A large number of patient studies were performed and will be described in detail in a subsequent report. Upper and lower limits of normal for males and post-menopausal females were lower than those for pre-menopausal females.

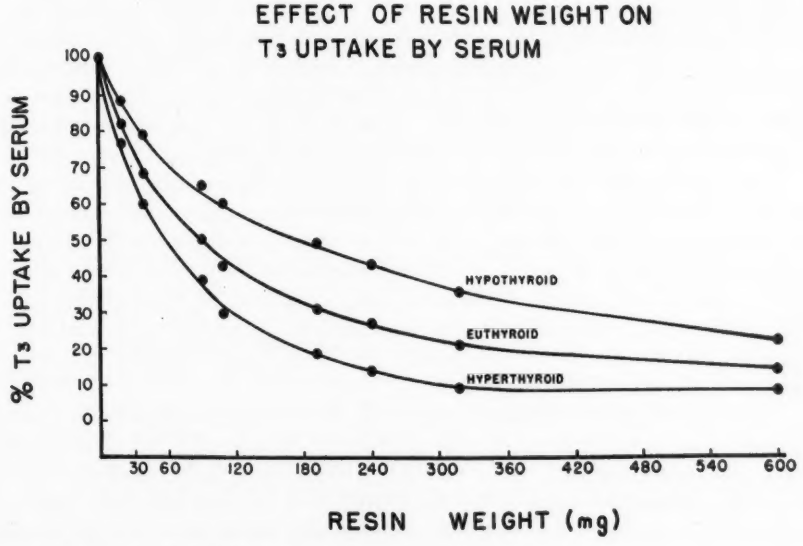


Fig. 6. Effect of resin weight on T_3 uptake by serum.

In the absence of interfering drugs (salicylates, diphenylhydantoin, etc.) or of abnormalities of binding proteins, (pregnancy, estrogen therapy, androgen therapy, cirrhosis, nephrosis, metastatic malignancy) excellent correlation with clinical states was obtained.

Normal values of the TPDI for males were 44-54 per cent with a mean of 49 per cent and a S.D. of 2.5 per cent. Normal values for pre-menopausal females were 46 to 56 per cent with a mean of 51 per cent and a S.D. of 2.5 per cent.

The mean value for post-menopausal females was 49 per cent with a S.D. of 3 per cent. The distribution of values in this group seemed to suggest a heterogenous population in which some individuals might still be secreting estrogen. It seems reasonable to assume that the difference in T^3 uptake values between euthyroid males and euthyroid pre-menopausal females is an estrogen effect.

DISCUSSION

There is little doubt that the T_3 uptake tests are valuable measurements of thyroid function. However, because of technical problems their usefulness has been limited. The Hamolsky test is still performed with satisfaction in many laboratories but the test is time-consuming and has inherent disadvantages. The methods that are based on the use of resin as the competitive acceptor of T_3 have not been perfected. There is little, if any, agreement as to the best method to be used. Previously described methods employ procedures of resin preparation and dispensing that are time-consuming or unnecessary. In contradistinction to our findings, improvement in discrimination between groups has been attributed to specific conditions of incubation (6) as well as to the use of certain buffers (6,8). The use of granular type resins has been said to result in unavoidable day to day variations (5).

We have found that dry resin can be rapidly and accurately measured in the dry state, but excessive drying must be avoided. Overly dried resin shatter upon rehydration and result in higher resin efficiency and reduced accuracy. In the absence of shattering uniform resin efficiency is obtained, particularly when large numbers of test vials are prepared from the same resin source.

The uptake efficiency of resin will vary when the moisture content of the dry resin is allowed to fluctuate markedly before the addition of trismaleate buffer. Differences in resin efficiency may also occur with variations in the degree of cross-linking from lot to lot. In addition, variations in average diameter of resin beads within a given mesh range will cause variations in resin uptake. All of these causes for variations can be circumvented by preparing large numbers of test vials that can be stored indefinitely. No unexplained variation in resin efficiency has been noted with our method.

The reproducibility of this test is due in part to accurate dispensing of resin portions. The use of a diluent, tris-maleate buffer, has also reduced or eliminated several causes for variations. It allows the preparation of large numbers of vials that can be depended upon to have a highly uniform resin efficiency. The expanded fluid volume ensures that complete mixing of resin and serum will occur during the incubating period and variations in counting efficiency are reduced by

ensuring a uniform counting geometry. The presence of 4 ml of supernate (tris-maleate plus serum) in the test vial facilitates the withdrawal of a 2 ml aliquot when incubation is completed. The use of a buffer has also improved this test by minimizing fluctuations in pH of the serum.

The I^{131}-labeled T_3 preparations available from commercial suppliers will contain variable amounts of impurities (I^{131}, I^{131}-T_4, and other unidentified impurities (11). We have found as much as 45 per cent I^{131}-T_4 present in one preparation. The presence of these impurities causes unavoidable fluctuations in T_3 uptake values. In addition, T_3 preparation will deteriorate in time. We have noted consistantly stable results during the first two weeks following the assay date of the preparations. Dilution, exposure to light, or heat may accelerate the deterioration of T_3. The use of a five per cent albumin solution has been effective in delaying this deterioration (6).

The solution to the problem of fluctuations of values has been the employment of control serum. In our method, significant variations in T_3 uptake of control serum should occur only when a new T_3 preparation is being used for the first time. Thereafter, large variations will indicate the presence of errors in technique or of deterioration of the I^{131}-T_3.

Discrimination between normal and hypothyroid patients will be best when the standard serum uptake is near the value of 35-40 per cent. The observations that discrimination between hypothyroid T_3 uptakes and normal T_3 uptakes is poor has been made repeatedly (8). It is to be noted that all the current resin methods operate outside the "ideal" range. Poor discrimination might also be related to the previously unrecognized difference in normal values between males and females.

For convenience, this method can be modified to measure the uptake of 1 ml rather than 2 ml of serum. Similarly the tube rotator can be used in laboratories that do not have access to an incubator shaker.

Since the range of normal is small when compared to the standard deviation of the technique, it is essential, whenever possible, to perform duplicate determinations. It is also desirable to perform 4-6 determinations on control serum.

SUMMARY

A study of the factors which influence the sensitivity and variability of a test which measures T_3 uptake of resin has been made. Dried resin can be simply and rapidly dispensed for use in this test. Aberrant results will occur when drying is excessive or when resin is allowed to reabsorb variable amounts of moisture. In addition, variations in resin particle size will affect the uptake efficiency per unit weight of resin. When these factors are acknowledged and controlled, large numbers of vials containing resin and tris buffer can be prepared and can be expected to have highly uniform uptake efficiency.

Variations in purity of T_3 shipments cause unavoidable fluctuations of T_3 uptakes, but each shipment can be depended upon to give uniform results for at least two weeks.

The sensitivity of the test is a function of the level of the per cent uptake by pooled normal serum. When uptakes of pooled normal serum fall near the extremes (0 or 100%) the spread between normal and abnormal values is diminished. This occurs regardless of the methods employed in measuring the uptake.

Over 4000 test on poled serum and 300 tests in duplicate on 270 patients were performed. Males and post-menopausal females had normal values that were lower than those for pre-menopausal females. There was a good discrimination between normal and abnormal groups.

ACKNOWLEDGEMENT

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Four Channel Magnetic Tape Recording and Digital Analysis of Radio-Hippuran Renal Function Tests in Normal Subjects[1,2,3]

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INTRODUCTION

The exchange of a tracer between different body compartments and its final release from the body is best characterized by a sum of exponential curves. If the count-rate of a radioactive tracer decreases exponentially with time, a fixed fraction of the amount present is eliminated per time interval. The half-time of the exponential function is the time it takes to release half of the material present at a certain time.

While studying the excretion of I^{131}-labeled Hippuran by the kidneys, it appeared important to investigate if the excretion rate can be expressed as a sum of exponential functions and if so to determine the number of exponentials and their half-times. Furthermore, a comparison of the retention of radio-Hippuran within the renal areas with retention in other body sites might yield additional information concerning the mechanism of Hippuran excretion.

The majority of the I^{131}-Hippuran renal function tests are terminated at a time when about one-third of the administered dose still remains in the body (1). It became apparent that more complete data were required for the analysis of the excretion curve. However, 20 to 30 minutes after the administration of the Hippuran its release becomes so slow that standard count-rate meters and recorders fail to yield accurate information. On linear display small percentage changes of count-rate cannot be recognized. Therefore, magnetic tape recording (2) of the scintillation pulses was used. This allows storing the pulses from four detectors placed over different body sites and multiple read-out of the data for an accurate analysis not only of slow changes in count-rate but also of the rapid changes occurring at the beginning of the Hippuran renal function test.

The paper will describe this new method of data preservation and reproduc-

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[1]Presented at the Ninth Annual Meeting of the Society of Nuclear Medicine, June 30, 1962, Dallas, Texas.

[2]From the Radioisotope and Medical Services, Boston Veterans Administration Hospital, the Robert Dawson Evans Memorial, Massachusetts Memorial Hospitals, and the Department of Medicine, Boston University School of Medicine, Boston, Mass.

[3]Supported in part by USPHS Grants HE 0658-02(5RC) and HE 05571-03 from the National Heart Institute.

tion. A consistent and complete analysis will be given for the radio-Hippuran turnover-rates in normal human subjects.

METHODS

A magnetic tape system[1] preserves the time sequence of the pulses from four scintillation counters. The pulses are recorded on four parallel tracks on ¼-inch magnetic tape. Tape speeds of 3.75, 7.50, 15 and 30 inches per second are provided for recording or read-out. Read-out tape speeds faster or slower than the recording speed produces contraction or expansion of the time axis while maintaining the time relationship between the curves from the four detectors.

The tape can be replayed as often as necessary in order to display the data in different forms. By using a count-rate meter and TY-plotter,[2] useful superimposition of a number of curves can be obtained on a single graph.

For quantitative analysis of an individual curve, maximum accuracy for counting the recorded pulses is obtained by scaling the pulses for fixed time intervals. For this purpose a 400-channel magnetic core analyzer[3] is employed in its multiscaler mode with automatic print-out of the resulting counts per time interval. Integration time intervals of 4 and 20 seconds are used in these studies. The digital data thus obtained are free of any distortions caused by the read-out method.

Four scintillation detectors are placed normal to the skin over the two renal areas, the left infraclavicular area and either the precordium or suprapubic area. The sodium iodide crystals are recessed 1½ inches in a straight bore collimator with a 1½-inch diameter opening. The sensitivity of the detectors are matched with an I^{131} source and back-scatter radiation is eliminated by a lower level discriminator.

Following the injection of 60-80 μc I^{131}-Hippuran, pulses were recorded from four body sites for 100 minutes. During this time the subjects voided at about 20 minute intervals, preventing significant contribution to renal area radioactivity from a high bladder concentration. The magnetic tape recording continued uninterrupted to preserve the time base. All urine passed from the time of injection through the next day was collected fractionally and the percentage of the dose excreted in each sample was determined. In some subjects the activity remaining in the body was measured at intervals up to 50 hours with a body counter (3).

Ascending chromatographic analysis of the administered Hippuran was performed in butanol, acetic acid and water (75:10:15). Chromatograms were analyzed in a gas flow strip counter and each spot was quantitated.

RESULTS

Complete data of two normal subjects served to delineate the processes involved in the release of I^{131}-Hippuran from the body. Both subjects were clinically free of cardiovascular and renal disease and were hospitalized for the treatment

[1]Transicord, Atomium Corp., Billerica, Mass.
[2]T-Y Recorder, Houston Instrument Corp., Houston, Texas.
[3]Model 402, Technical Measurement Corp., North Haven, Connecticut.

of psoriasis. One subject was 57 years of age and was studied repeatedly on consecutive days under varied physiological conditions; the other was 37 years. In three additional healthy volunteers body retention, calculated from urine collection and body counting data, was determined. The recovery of nearly 100 per cent of the administered Hippuran with less than 0.1 per cent in the last sample at 48 hours attest to the completeness of the collections.

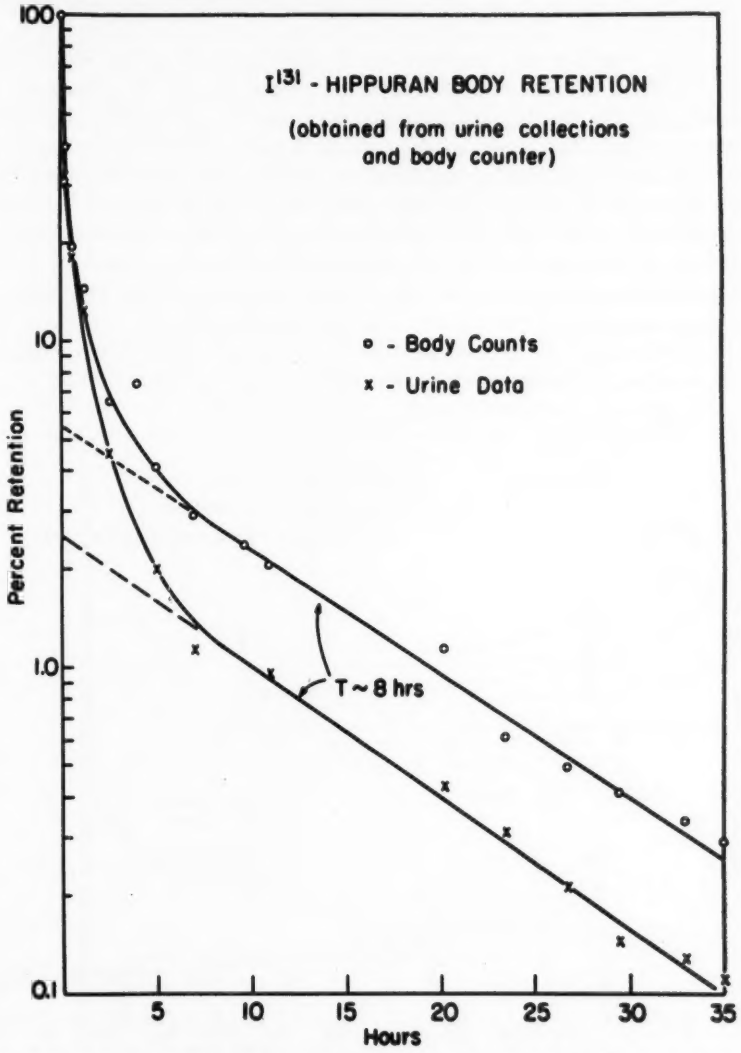

Fig. 1. Retention of I^{131}-Hippuran in the body. The data obtained with the body counter are less accurate than those calculated from urine collections since the count-rate depends on the distribution of the radioactivity within the body. The final half-time (T) of excretion as determined by the two sets of measurements are the same.

A typical radio-Hippuran body retention curve constructed from both urine collection and body counting data is presented in Figure 1. In this case, seven hours after injection a single exponential approximates the rate of excretion of the remaining Hippuran. The half time (T) of this exponential ranged from 4 to 13 hours in a small group of subjects. Extrapolation of this exponential back to the time of injection yields the per cent of the dose excreted at this rate. The observed values varied from 3 to 6 per cent of the administered dose in this component.

An analog display of a single study of subject 1 is shown in Figure 2. The count-rate curves of the two renal areas, the precordial and infraclavicular area are shown, and the first 18 minutes of the same curves are shown in addition on an expanded scale. The characteristic pattern of rising activity in the renal areas followed by rapid and then slow descent is evident. The precordium and infraclavicular site yield curves with initial spikes reflecting passage of the injected bolus, followed immediately by descending curves similar to those of the renal areas. After 20 minutes the four curves appear to fall at equal rates.

The infraclavicular area was chosen from many body sites investigated in uninephrectomized patients as giving the closest approximation to the count-rate from the nephrectomized side at any time. In 10 patients the nephrectomized and infraclavicular areas yielded curves identical in slope after the first 2-4 minutes,

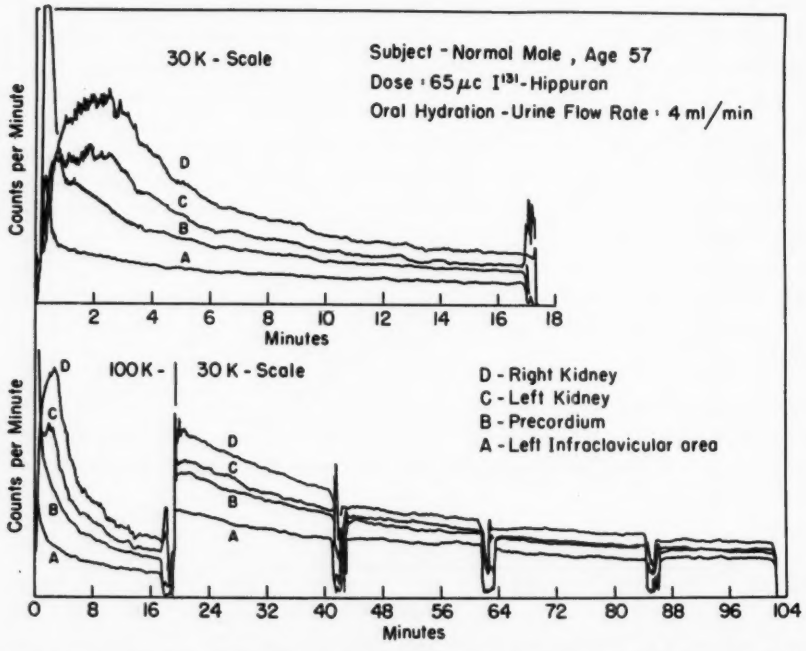
30 K - Scale
Subject - Normal Male , Age 57
Dose : 65 μc I¹³¹-Hippuran
Oral Hydration - Urine Flow Rate : 4 ml/min
Counts per Minute
D
C
B
A
2 4 6 8 10 12 14 16 18
Minutes
100 K - | 30 K - Scale
D - Right Kidney
C - Left Kidney
B - Precordium
A - Left Infraclavicular area
0 8 16 24 32 40 48 56 64 72 80 88 96 104
Minutes

Fig. 2. Analog display of count-rates simultaneously recorded on magnetic tape from four body sites for 100 minutes. The first 18 minutes are shown in addition on an expanded time scale. The recording was not interrupted when the patient voided at twenty minute intervals.

differing in magnitude by no more than 20 per cent. Figure 3 shows one such study.

The digital analysis of the data of the right renal area, the precordium, and the infraclavicular area of the study shown in Figure 2 are presented in Figures 4-6. The counts for each 20 second interval of the 100 minutes counting time, yielding 300 points for each curve, are plotted on a logarithmic scale versus time on a linear scale. Since the data do not scatter unduly, smooth curves are drawn through the points with little ambiguity. Close examination of these curves show no part to be a straight line. With the present accuracy of the data it is discovered that even the tail of the curve is concave although deviation from a straight line is small. The urine collection data (Fig. 1) predict that an exponential fit can be expected only after several hours.

In order to resolve the original data into a sum of exponentials, we proceeded as follows. The per cent of the administered dose remaining in the body at 100 minutes is known from the urine collection data (Fig. 1). The counts per 20 seconds of each body site are also known (Figs. 4-6), allowing its conversion into per cent retained. Finally, the percentage and the half-time of the *final* exponential for the Hippuran excretion can be taken from the body retention curve. The exponential curve representing this slowest component of Hippuran release was then drawn into Figures 4-6. Its half-time was 12 hours and it contains about 5 per cent of the dose when extrapolated back to the time of administration.

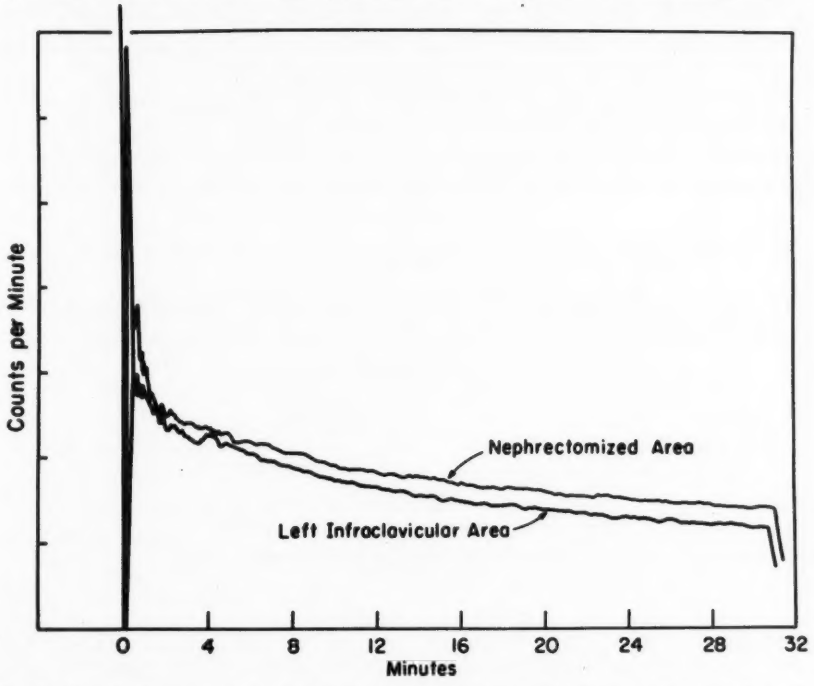

Fig. 3. Count-rate curves from infraclavicular and nephrectomized areas of one patient after injection of I^{131}-Hippuran. The two curves were found to be quite similar for each patient in a group of 10 uninephrectomized patients.

The exponential count-rates of the long term component were subtracted from the original data (Figs. 4-6). This results in the values shown by crosses which fall on straight lines for the last 35 minutes with only minor deviations of the points. The difference between the crosses and the extrapolation of the straight line yields the values given by the open circles. Again, a straight line can be fitted to the data without much ambiguity. Finally, the difference between its extrapolation and the open circle values can be accounted for by a fourth exponential.

Since the analysis yields the same exponential components over the precordium and infraclavicular area as over the renal areas, each site must reflect clearance of I^{131}-Hippuran from the body. Therefore, it should be possible to obtain the same information from an analysis of the rate of excretion of the radioactivity by measurements over the bladder. The results of such an attempt with subject 2 is shown in Figure 7.

A body retention curve, which can be measured directly from the other body areas, has to be derived in the case of the bladder measurements. Furthermore, the accumulation in the bladder was interrupted several times by voiding. Therefore, a total accumulation curve was constructed first. The residual count-rate at the time of voiding was regarded as arising from the tissues surrounding the bladder. This tissue background decreases with time as seen in Figure 7; it was subtracted from the total accumulative counts. Finally, the body retention curve was obtained by subtracting the cumulative counts from the count-rate to be expected if the total administered dose were concentrated in the bladder. The analysis of the retention curve is the same as in Figures 4-6.

Table I compiles the half-time values of the exponential components obtained from the analysis of the data from the two subjects. The accuracy of each additionally derived component depends on that of the prior ones, and with additive errors, the values of the fastest components are only approximate. The half-

TABLE I

HALF-TIMES OF EXPONENTIAL COMPONENTS OBTAINED FROM THE ANALYSIS OF COUNTS PER 20 SECONDS FROM THREE BODY SITES OF TWO DIFFERENT SUBJECTS (FIGS. 4-7)

Subject 1	*Components*			
Body site	*1*	*2*	*3*	*4*
Chest	1.7 min.	16.3 min.	50 min.	12 hrs.
Kidney	2.0 min.	10.0 min.	50 min.	12 hrs.
Precordium	1.3 min.	7.5 min.	40.7 min.	12 hrs.
Subject 2	*Components*			
Body site	*1*	*2*	*3*	*4*
Chest	1.8 min.	9.5 min.	79 min.	4 hrs.
Kidney	3.3 min.	9.7 min.	67 min.	4 hrs.
Bladder	1.2 min.	6.0 min.	52 min.	4 hrs.

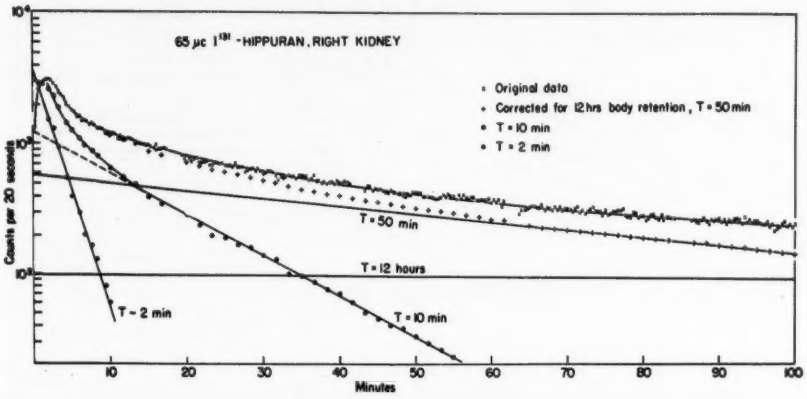
65 μc I131 - HIPPURAN, RIGHT KIDNEY
Original data
Corrected for 12 hrs body retention, T = 50 min
T = 10 min
T = 2 min
T = 50 min
T = 12 hours
T = 2 min
T = 10 min
Counts per 20 seconds
Minutes

Fig. 4. Counts per 20 seconds from right renal area for 100 minute magnetic tape recording. The slow component with a 12 hour half-time is subtracted from the original data (net counts). The derived data can be accounted for by three exponential curves with half-times (T) of about 50, 10 and 2 minutes.

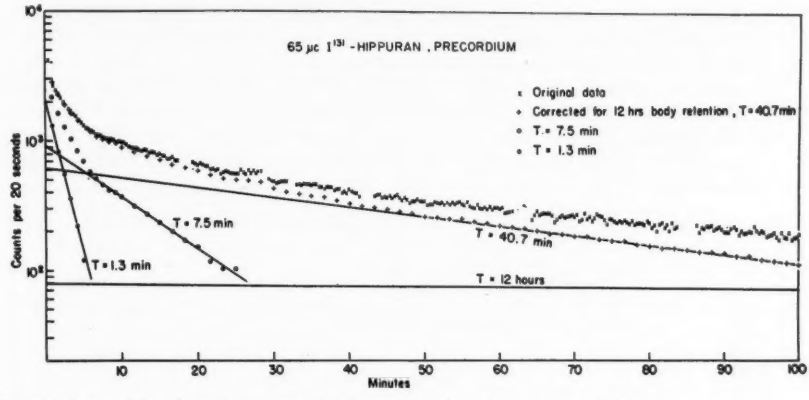
65 μc I131 - HIPPURAN, PRECORDIUM
Original data
Corrected for 12 hrs body retention, T = 40.7 min
T = 7.5 min
T = 1.3 min
T = 7.5 min
T = 40.7 min
T = 1.3 min
T = 12 hours
Counts per 20 seconds
Minutes

Fig. 5. Same analysis as in Figure 4 for counts taken from precordial area.

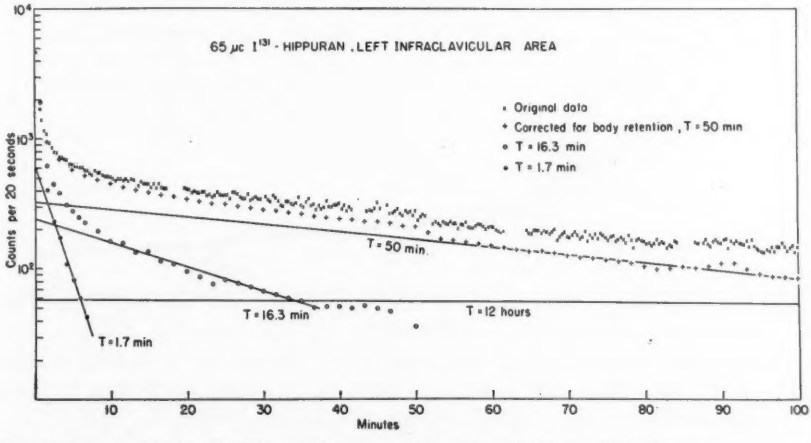
65 μc I131 - HIPPURAN, LEFT INFRACLAVICULAR AREA
Original data
Corrected for body retention, T = 50 min
T = 16.3 min
T = 1.7 min
T = 50 min
T = 16.3 min
T = 12 hours
T = 1.7 min
Counts per 20 seconds
Minutes

Fig. 6. Same analysis as in Figure 4 for counts taken from left infraclavicular area.

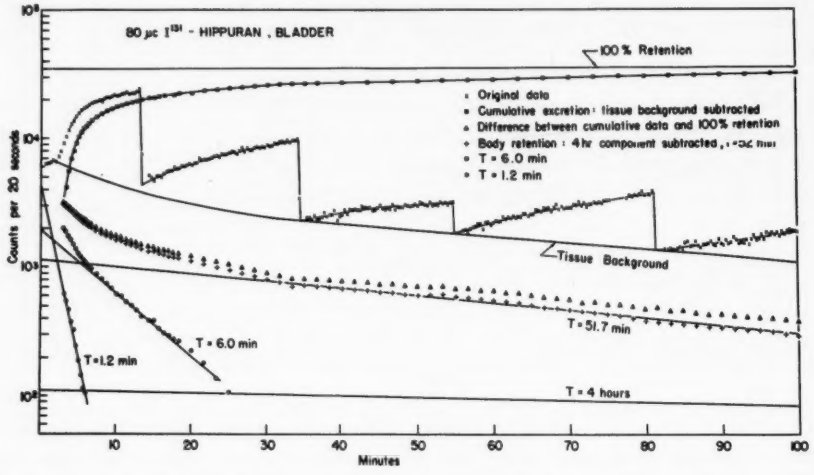
80 μc I131 - HIPPURAN , BLADDER
100 % Retention
Original data
Cumulative excretion : tissue background subtracted
Difference between cumulative data and 100% retention
Body retention : 4 hr component subtracted, T = 50 min
T = 6.0 min
T = 1.2 min
Tissue Background
T = 51.7 min
T = 6.0 min
T = 1.2 min
T = 4 hours
Counts per 20 seconds
Minutes

Fig. 7. Analysis of counts from suprapubic area. The original data represent the accumulation of I^{131}-Hippuran in the bladder. At each voiding the count-rate drops to a level determined by the radioactivity of the tissues surrounding the bladder. This tissue background was subtracted from the cumulative counts from the bladder. Finally, from the percentage of the dose excreted at 100 minutes the counts per 20 seconds corresponding to 100 per cent of the dose in the bladder was established. The difference between the cumulative counts and the 100 per cent level yields the body retention as a function of time. The retention curve was than analyzed as that in Figure 4.

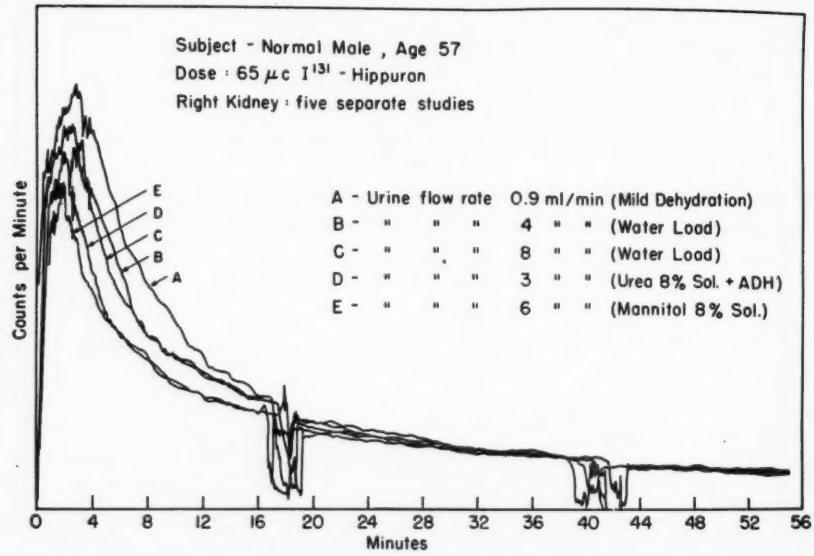
Subject - Normal Male , Age 57
Dose : 65 μc I131 - Hippuran
Right Kidney : five separate studies
A - Urine flow rate 0.9 ml/min (Mild Dehydration)
B - " " " 4 " " (Water Load)
C - " " " 8 " " (Water Load)
D - " " " 3 " " (Urea 8% Sol. + ADH)
E - " " " 6 " " (Mannitol 8% Sol.)
Counts per Minute
Minutes

Fig. 8. Count-rate curves from right renal area of one subject after administration of 65 μc I^{131}-Hippuran on each of five consecutive days. Variation of the urine flow rates and the infusion of two diuretics affected only the early parts of the curves.

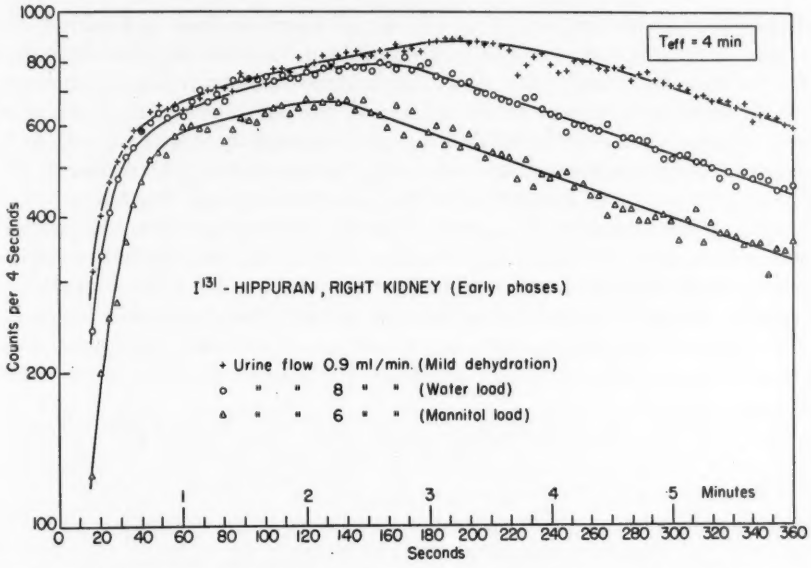
Teff = 4 min
I131 - HIPPURAN, RIGHT KIDNEY (Early phases)
+ Urine flow 0.9 ml/min. (Mild dehydration)
o " " 8 " " (Water load)
Δ " " 6 " " (Mannitol load)
Counts per 4 Seconds
Seconds
Minutes

Fig. 9. Semi-logarithmic plot of digital read-out of three of the curves shown in Figure 8. The time when the decrease of the count-rate starts depends on the physiological conditions of the test.

times of successive components differ from each other by at least a factor of five and therefore could be delineated with reasonable accuracy in few studies.

The above measurements were performed under moderate hydration as is standard for the Hippuran renal function studies in many laboratories. To evaluate the possible variation of the excretion rates due to changes of physiological conditions subject 1 was studied five times with identical doses of radio-Hip-

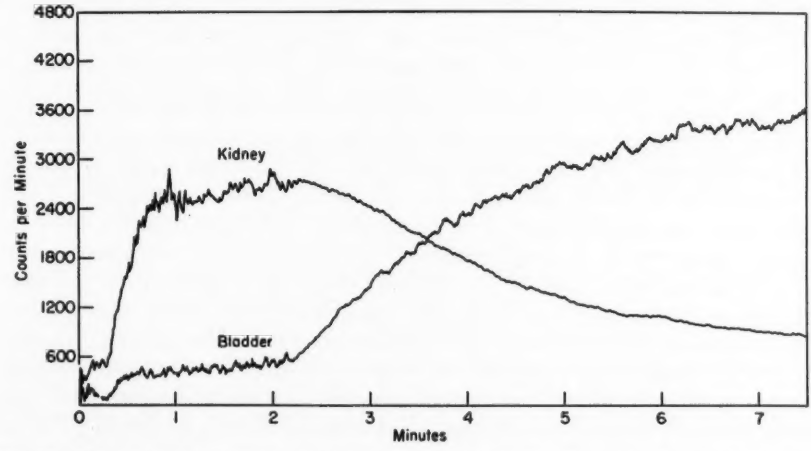

Fig. 10. Early phase of kidney and bladder curves. Note the sharp rise in count-rate from the bladder at the time the maximum count-rate is reached from the kidney.

puran: (a) at basal urine flow of 0.9 ml/min; (b) at urine flows of 4 ml/min and (c) 9 ml/min produced by oral water loads; (d) at 6 ml/min produced by I. V. 8 per cent Mannitol at 6 ml/min; (e) at 3 ml/min produced by I. V. 8 per cent urea with Pitressin[1] at 7 ml/min and 4 mu/min. It has been shown that the time of renal tubular passage of the labeled material, particularly if it is delayed as in renal arterial constriction, is shortened during osmotic diuresis (4). Analog curves of the right renal area from these studies are superimposed for comparison in Figure 8. Early differences are apparent but after 20 minutes all curves superimpose. Peak activity is highest and is reached latest with basal hydration. Water loading causes the peak to occur somewhat sooner and to be of lesser amplitude, but there is identity of the curves obtained at urine flow rates of 4 and 9/ml. Urea-ADH and Mannitol loading result in still lower peaks occurring even sooner although the urine flow rates were adjusted to fall between those of the two water loading conditions.

For a detailed study of the early phases of the test, the first 400 seconds of the data in Figure 8 obtained with basal urine flow, moderate hydration and Mannitol load have been integrated at four second intervals and plotted semilogarithmically (Fig. 9). The initial 2-3 minutes of the descending portion approximate an exponential component with an apparent or "effective" half-time of 4 minutes. Analysis of the complete data (Fig. 4) yielded an initial half-time of about two minutes. The discrepancy reflects inclusion in the "effective" half-time of other significant components with longer half-times.

While the kidney area shows an initial period of accumulation not seen in other body sites, our analysis of the excretion curves shows four similar exponential components in both renal and extra-renal areas. In over 150 routine studies in which bladder area curves were obtained no activity above regional tissue background appears until at least one of the kidneys reaches peak and starts down. Figure 10 illustrates this phenomenon.

Ascending chromatographic analysis of the Hippuran used in these studies showed 4-5 per cent of non-Hippuran radioactivity, the major part migrating as free iodide.

DISCUSSION

The excretion curves of radio-Hippuran were resolved into four distinctly different exponential components with half-times varying between a few minutes and several hours. The most rapid component with the largest apparent volume of distribution probably reflects the rapidly falling blood concentration of the radioisotope due to simultaneous renal clearance and rapid diffusion from the vascular compartment. As renal clearance continues, blood concentration eventually diminishes below that of the extravascular spaces resulting in net back diffusion of the radioactivity. Back diffusion from various body compartments will produce slower components. Extracellular space and red cells may constitute one readily exchanging compartment, while more slowly exchanging compartments may include intracellular spaces or cerebro-spinal fluid which had been shown to actively concentrate Hippuran-like compounds from the blood (5). The

[1]Parke, Davis & Company.

wide variation in the half-time of the slowest component indicates highly variable clearance which may reflect non-Hippuran impurities or breakdown products.

Perhaps surprising is the similarity of the rates of descent of the renal area curves with those of other body sites. That the renal curves preserve so well the time-concentration relationship of the rest of the body indicates that while passage of the radioisotope through the kidney to the ureter introduces a renal delay, there is, in normal well-hydrated subjects, no significant pooling of the radioisotope in the renal pelvis. The initial period of accumulation of I^{131}-Hippuran in the renal areas results from its continuing filtration and tubular secretion until the more concentrated material initially extracted completes passage through the tubular system and abruptly leaves the "view" of the renal detector to appear in the bladder.

SUMMARY

The excretion of I^{131}-Hippuran from the kidney areas and from other body sites was followed in normal subjects for 100 minutes. The counts from four scintillation detectors placed close to the four body sites are permanently stored on magnetic tape. To compare the results from different body sites or tests, data are read-out from the magnetic tape through a count-rate meter and plotted by a T-Y plotter, allowing superimposition of many curves on a single graph. Urine collections were made for about 48 hours with recovery of 100 per cent of the injected dose.

The data from the magnetic tape are also read-out by integrating the counts for selected time intervals (4 and 20 seconds) by a multiscaler. These digital data are then plotted semilogarithmically for quantitative analysis. The excretion data for each body site could be accounted for by four exponential components with half-times of about 2, 10, and 50 minutes and one of several hours.

These exponential components must reflect both renal clearance and redistribution of the Hippuran through several body compartments. Since the renal area data indicate no additional exponential of discharge, the release of the Hippuran by the kidneys is only delayed relative to that by other body sites, resulting in a period of rising count-rate not found elsewhere. The time when the maximum count-rate occurred and its magnitude for a fixed dose of I^{131}-Hippuran could be influenced by the state of hydration and the administration of osmotic diuretics.

Storage of scintillation pulses on magnetic tape provided the necessary flexibility to handle the data for an analysis of renal function which could not be achieved otherwise.

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3. Hine, G. J., Jagger, P. I., and Burrows, B. A.: Measurement of Body Radioactivity for Studies of Sodium Metabolism. *J. Lab. & Clin. Med.* **55**:476, 1960.
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5. Papenheimer, J. R., Heisey, S. R., and Jordan, E. F.: Active Transport of Diodrast and Phenolsulfonphthalein from Cerebrospinal Fluid to Blood. *Am. J. Physiology* **200**:1, 1961.

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Distribution of Some Radioiodinated Tetracyclines In Animals[1]

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Omaha, Nebraska

INTRODUCTION

Many investigators have shown that the tetracycline family of antibiotics localizes in tumors and newly forming bone (1-6). The localization of tetracycline in tumors prompted us to attempt to label tetracycline with a radioactive element in hopes that it might prove useful for diagnosing and possibly treating patients with tumors (7).

The synthesis of pyrrolidino-methyl-tetracycline (8, 9) and the identification of its structure (10) has led to our development of N-(4-iodopyrazole-methyl)-tetracycline. This paper, then, compares the *in vivo* distribution of N-(4-radioiodopyrazole-methyl)-tetracycline with 9-radioiodo-6-demethyl-6-deoxy-tetracycline, and the pyrrolidino-methyl derivative of 9-radioiodo-6-demethyl-6-deoxy-tetracycline in mice with tumors and reports the uptake in dog and mouse liver of N-(4-radioiodopyrazole-methyl)-tetracycline.

METHODS AND MATERIALS

Synthesis of 4-iodopyrazole: Into a 500 ml round-bottom flask are added 100 ml H_2O, 2.5 gm of pyrazole, 4.5 gm of sodium bicarbonate, 200 ml methanol, and 9.5 gm iodine. The reaction mixture is refluxed until the solution decolorizes to clear or to a pale yellow. Most of the water and methanol are removed *in vacuo*. The remaining solution, approximately 20-40 ml, is cooled in an ice bath and the crystals collected by filtration. The product melts at 105° to 107° C (uncorrected). The yield is 78 per cent after recrystallizing once from water.

		Calculated	Found
Analysis:	Percent C	18.5	18.5
	Percent H	1.5	1.5
	Percent N	14.5	14.3
	Percent I	65.5	65.5

[1]From the Radioisotope Service, Veterans Administration Hospital, Omaha, Nebraska.

Exchange of I-127 on 4-iodopyrazole for I-131: To 3 gm twice recrystallized 4-iodopyrazole is added 100 ml of water. The pH is adjusted to 2.0 with HCl, and carrier-free I-131 as sodium iodide added. The mixture is refluxed for one hour, after which the solution is concentrated to 20 ml *in vacuo*. The solution is neutralized with sodium bicarbonate, cooled in an ice bath, and the crystals collected by filtration.

Preparation of N-(4-iodopyrazole-methyl)-tetracycline: (Fig. 1) One gm of 4-iodopyrazole, 2.5 gm of tetracycline, 50 ml of T-butanol, and 1.0 ml of 37 per cent formaldehyde are refluxed for 16 hours on a steam bath. The solution is cooled to room temperature, and the product, collected by filtration, is purified by column chromatography on Celite (H_2O-HCl-pH 2 butanol-chloroform) (11). The first 200 ml of colored eluate to come from the column is concentrated *in vacuo* to dryness (40°C) and reprecipitated from n-butanol. This product decomposes at 160° to 177° C.

The 9-iodo-6-demethyl-6-deoxytetracycline was synthesized by a procedure obtained from another laboratory (12). The N-(pyrrolidino-methyl)-6-deoxy-6-demethyl-9-iodotetracycline was synthesized after the procedure of Gottstein *et al.* (10, 13).

Experimental Groups of Mice: C3H spontaneous mammary-tumor-bearing mice were used for this study. Groups 1 through 4 consisted of 40 mice each. A radioactive material was injected intraperitoneally into each mouse once daily for 3 days. Each of the first group received 1 mg of N-(4-radioiodopyrazole-methyl)-tetracycline (activity 1.2 X 10^6 cpm/mg). Each of the second group received carrier-free sodium radioiodide (1.2 X 10^6 cpm). Each of the third group received 1 mg. of 4-radioiodopyrazole (0.6 X 10^6 cpm/mgm). Each of the fourth group received carrier-free sodium radioiodide (0.6 X 10^6 cpm). Ten mice from each of the 4 groups were sacrificed (at 24, 72, 120 and 168 hours after the last injection) by a sharp blow at the back of the head. They were quickly exsanguinated by opening the thorax and cutting the aortic arch. Blood was collected by allowing it to run into a preweighed plastic counting tube, and the amount

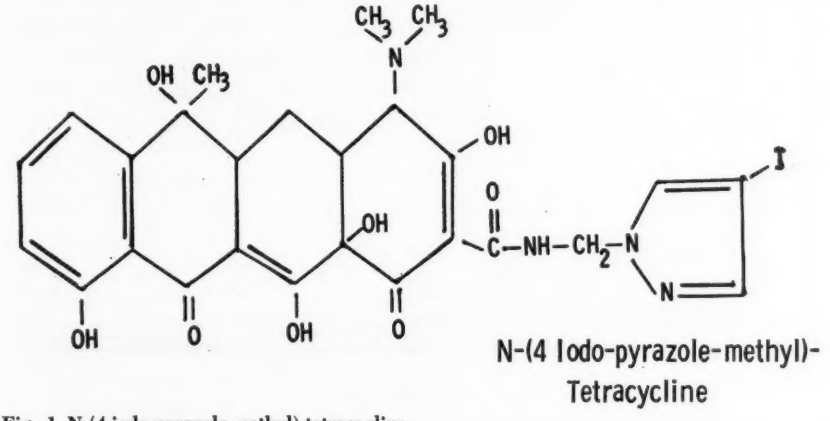

Fig. 1 N-(4-iodo-pyrazole-methyl)-tetracycline.

determined by difference in weight of the full minus the empty tube. The gluteus maximus muscle, femur, liver, and tumor were excised from each mouse and each tissue weighed. The thyroids were excised and these as well as the individual tissues were placed in separate plastic test tubes for counting in a well-type scintillation counter (30% efficiency). The results were recorded as net counts per minute per milligram of wet tissue.

Groups 5 through 7 consisted of 30 mice each. Each of the fifth group received 0.5 mgm of 9-radioiodo-6-demethyl-6-deoxy-tetracycline (8.2×10^5 cpm/0.5 mgm). Each of the sixth group received 0.46 mgm of N-(pyrrolidinomethyl)-6-deoxy-6-demethyl-9-radioiodo-tetracycline (8.2×10^5 cpm/0.46 mgm.). Each of the seventh group received carrier-free sodium radioiodide (8.2×10^5 cpm). The mice in these 3 groups were sacrificed at 24, 48 and 96 hours after the last injection. The method of sacrifice and collection of tissues were the same as that for the preceding groups.

Dog Liver Scintiscans: The 5 mongrel dogs weighed from 18 to 30 kg. Each dog received, I.V., 10 mgm of N-(4-radioiodopyrazole-methyl)-tetracycline, in propylene glycol, per kg of body weight (the specific gravity of this drug varied from dog to dog). Scintigrams were made by passing a scintiscanner probe over the liver area of dogs anesthetized with nembutal and lying on their left side. Liver scintigrams were made from one dog at 4, 24, and 48 hours after receiving this drug: the other liver scintigrams were made at either 4 or 8 hours after injection of the radioactive drug.

Blood disappearance studies: Each of three different dogs received graded doses of 10, 20, and 40 mgm of N-(4-radiodopyrazole-methyl)-tetracycline per kg of body weight. Another dog was given, orally, 60 mgm of the radioiodo-

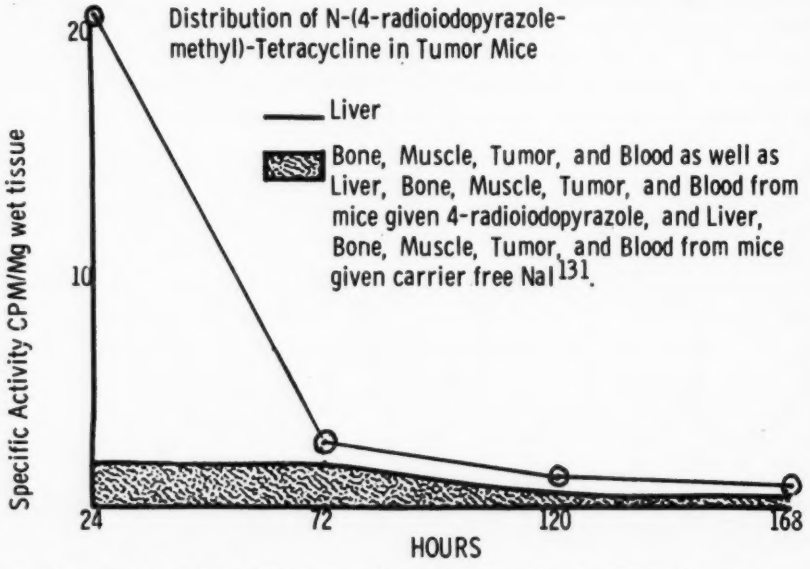
Distribution of N-(4-radioiodopyrazole-methyl)-Tetracycline in Tumor Mice
Liver
Bone, Muscle, Tumor, and Blood as well as Liver, Bone, Muscle, Tumor, and Blood from mice given 4-radioiodopyrazole, and Liver, Bone, Muscle, Tumor, and Blood from mice given carrier free NaI 131.
Specific Activity CPM/Mg wet tissue
20
10
24
72
120
168
HOURS

Fig. 2 Distribution of N-(4-radioiodopyrazole-methyl)-tetracycline in mice with tumors.

pyrazole tetracycline per kg of body weight. Blood was drawn from all the dogs at 2, 4, 6, 24, 48 and 72 hours and the amount of radioactivity contained in 1 ml of blood was determined using a well-type scintillation counter.

RESULTS AND DISCUSSION

The distribution of radioactivity in the muscle, femur, liver, tumor, thyroid and blood from mammary-tumor bearing mice, after the injections of N-(4-radio-

TABLE I

DISTRIBUTION OF RADIOIODOPYRAZOLE TETRACYCLINE IN MICE WITH MAMMARY TUMORS

Tissue	*10 Mice Given iodopyrazole Tetracycline*		*10 Mice Given Equal Amounts of Radioactivity (NaI) as Experimental Mice*		*Student t Values*
			24 Hours		
Muscle	1.53‡±	3.41*	.32 ±	.33	1.12 not sig.
Blood	.44 ±	.52	.23 ±	.26	1.13 not sig.
Tumor	1.21 ±	1.47	3.46 ±	8.95	.79 not sig.
Liver	20.34 ±	8.48	.19 ±	.11	7.51 sig.
Bone	.33 ±	.29	.37 ±	.44	.24 not sig.
Thyroid+	7,203.00 ±	3,466.00	32,598.00 ±	20,187.00	3.92 sig.
			72 Hours		
Muscle	1.77 ±	4.43	.19 ±	.36	1.12 not sig.
Blood	.11 ±	.05	.16 ±	.20	.65 not sig.
Tumor	1.40 ±	2.88	.31 ±	.49	.98 not sig.
Liver	2.55 ±	1.23	.12 ±	.05	6.22 sig.
Bone	1.59 ±	3.46	2.02 ±	4.17	.28 not sig.
Thyroid+	821.00 ±	329.00	18,855.00 ±	6,842.00	8.31 sig.
			120 Hours		
Muscle	.06 ±	.02	.07 ±	.04	1.03 not sig.
Blood	.06 ±	.02	.08 ±	.04	1.27 not sig.
Tumor	.04 ±	.07	.16 ±	.18	1.20 not sig.
Liver	1.29 ±	.53	.08 ±	.04	7.15 sig.
Bone	.13 ±	.07	.07 ±	.04	1.96 not sig.
Thyroid+	818.50 ±	310.60	17,324.00 ±	7,269.00	7.18 sig.
			168 Hours		
Muscle	.68 ±	1.40	.06 ±	.03	1.41 not sig.
Blood	.02 ±	.01	.06 ±	.04	3.06 sig.
Tumor	1.65 ±	4.97	.06 ±	.04	.83 not sig.
Liver	.38 ±	.16	.11 ±	.16	3.67 sig.
Bone	.04 ±	.04	.06 ±	.06	1.10 not sig.
Thyroid+	563.00 ±	2.40	12,354.00 ±	3,787.00	9.82 sig.

‡All values expressed as cpm/mgm wet tissue
*Standard deviation
+cpm contained in the thyroid gland

iodopyrazole-methyl)-tetracycline (iodopyrazole-tetracycline), indicates that this drug is preferentially taken up by the liver (Table I). The radioactivity in the liver indicates that the concentration of iodopyrazole-tetracycline is approximately 20 times greater here than in any of the other body tissues studied at this time (Fig. 2). The concentration is significant at greater than the 99.99 per cent

TABLE IA

DISTRIBUTION OF RADIOIODOPYRAZOLE IN MICE WITH MAMMARY TUMORS

Tissue	*Experimental 10 Mice Given Radio Iodo Pyrazole*	*Control 10 Mice Given Equal Amounts of Radioactivity (NaI) as Experimental Mice*	*Student t Values*
	24 Hours		
Muscle	.08‡[a] ± .04*	.64 ± .70	2.56 sig. @ .02 level
Blood	.21 ± .18	2.26 ± 3.83	1.70 not sig.
Tumor	.44 ± .29	3.40 ± 4.80	1.95 not sig.
Liver	.30 ± .24	.39 ± .12	.67 not sig.
Bone	.18 ± .13	.98 ± 1.52	1.64 not sig.
Thyroid+	8,657.00 ± 2,588.00	5,473.00 ± 7,735.00	1.15 not sig.
[a]9 Animals			
	72 Hours		
Muscle	.10 ± .05	.17 ± .11	1.72 not sig.
Blood	.09 ± .07	.43 ± .14	6.60 sig.
Tumor	1.15 ± 2.83	3.22 ± 8.72	.68 not sig.
Liver	.18 ± .10	.48 ± .19	4.33 sig.
Bone	.20 ± .04	.38 ± .53	1.07 not sig.
Thyroid+	1,255.00 ± 320.00	52,217.00 ± 24,604.00	6.55 sig.
	120 Hours		
Muscle	.04 ± .04	.16 ± .17	2.13 not sig.
Blood	.06 ± .04	.24 ± .11	4.90 sig.
Tumor	.37 ± .69	.42 ± .40	.18 not sig.
Liver	.15 ± .17	.23 ± .09	1.20 not sig.
Bone	.09 ± .06	.08 ± .06	.53 not sig.
Thyroid+	1,251.00 ± 431.00	20,322.00 ± 4,609.00	6.97 sig.
	168 Hours		
Muscle	.03 ± .03	.04 ± .02	.10 not sig.
Blood	.02 ± .02	.37 ± .37	2.66 sig. @ .02 level
Tumor	.14 ± .25	1.86 ± 3.21	1.53 not sig.
Liver	.03 ± .01	.20 ± .09	5.46 sig.
Bone	.08 ± .09	.03 ± .04	1.43 not sig.
Thyroid+	890.80 ± 322.00	30,104.00 ± 11,803.00	7.09 sig.

‡All values expressed as cpm/mgm wet tissue
*Standard deviation
+cpm contained in the thyroid gland

level. The mean of the tumor tissues is second highest, but is insignificant when compared to the remaining tissues. Large standard deviations occur from one tumor to another. This is probably due to the variation in the tumor tissue itself, which ranges from cystic to fibrotic, and also due to the uptake of I-131 as sodium iodide by the mammary gland. When tumors from mice, treated with radioiodopyrazole-tetracycline, are statistically compared to tumors from mice which were given 4-radioiodopyrazole and tumors from mice which received radioactive iodine as sodium iodide, no significant difference existed between them (Table I, IA, Fig. 2). The level of radioactivity in the liver of mice treated with iodopyrazole tetracycline is significantly higher than that found in the liver of the 2 control groups, *i.e.*, those mice receiving I-131 and 4-iodopyrazole. A statistical comparison between the 3 groups of the bone, muscle and blood indicates they are not significantly different.

The iodopyrazole tetracycline was chromatographically pure but elemental analysis indicated that it was impure. Repeated attempts to purify it have failed. Therefore, we utilized the animal's thyroid as an indicator for the radio-purity of the product. The data (Fig. 3) indicates that the product acts differently from radioiodine as sodium iodide. This difference is significant at the 99.99 per cent level. The radioiodine from both 4-radioiodopyrazole and radioiodopyrazole-tetracycline was taken up in identical amounts by the mouse thyroid. Since the 4-radioiodopyrazole used in the experiment was chemically pure and equal amounts of radioactivity were given each mouse, it is possible that either the

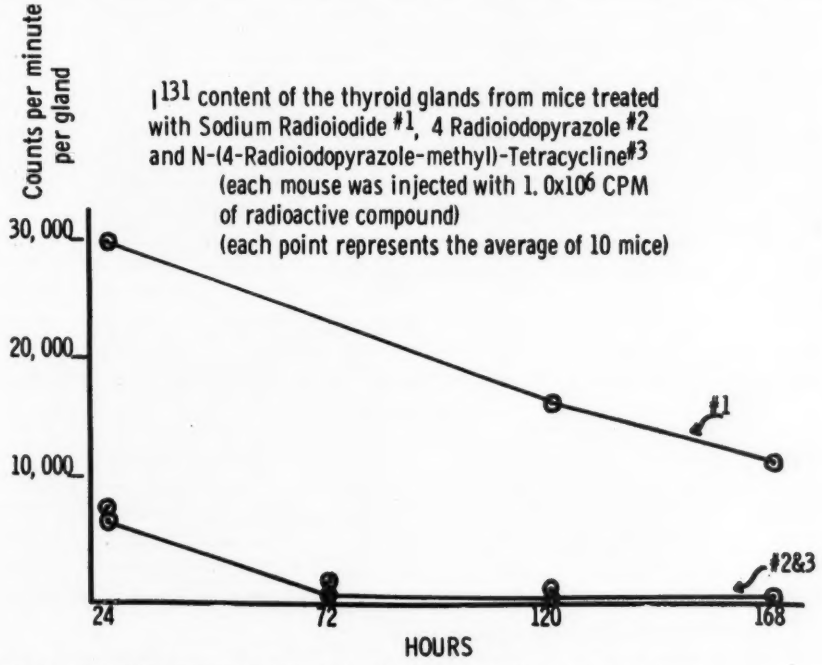

Fig. 3 Radioiodine content in thyroid gland after an injection of various drugs.

iodine was being split from 4-iodopyrazole or that the 4-iodopyrazole was being split from the tetracycline molecule; and then, that the 4-iodopyrazole was either being deiodinated or was being preferentially taken up by the thyroid. It is more likely that the two compounds were being deiodinated at the same rate, since the radioactive uptake in the thyroid, removed from mice given injections of iodopyrazole, and those given iodopyrazole tetracycline, were identical. We thus postulate that the iodine in this product was slowly removed *in vivo*; and if the drug is used in patients they should be pretreated with Lugol's solution.

The fact that this drug concentrates in the liver is not surprising since this is one of the main routes for tetracycline excretion (6). It was hoped that an insight into the distribution of tetracycline versus an N-amide-substituted tetracycline might be obtained, by using 9-radioiodo-6-demethyl-6-deoxy-tetracycline versus N-(pyrrolidino-methyl)-9-radioiodo-6-demethyl-6-deoxy-tetracy-

TABLE II

RADIOACTIVE TETRACYCLINES IN VARIOUS TISSUES FROM MICE WITH MAMMARY TUMORS

Tissue	*10 Mice Given 9-Iodo-6-Demethyl-6-Deoxytetracycline*		*10 Mice Given N-(Pyrrolidine-Methyl)-9-Iodo-6-Demethyl-6-Deoxytetracycline*		*10 Mice Given Equal Amounts of Radioactive (NaI) as Experimental Mice*	
			24 Hours			
Muscle	1.81‡±	.71*	5.23 ±	.99	.69 ±	.38
Blood	3.08 ±	1.76	10.75 ±	3.15	1.11 ±	.94
Tumor	7.69 ±	7.46	14.31 ±	5.15	3.29 ±	4.73
Liver	5.75 ±	3.98	29.84 ±	11.92	1.41 ±	.65
Bone	2.85 ±	1.34	8.17 ±	1.54	.48 ±	.44
Thyroid+	5,465.00 ±	4,772.00	9,495.00 ±	1,847.00	197,139.00 ±	68,016.00
			48 Hours			
Muscle	.81 ±	1.13	1.26 ±	.38	.69 ±	.90
Blood	.91 ±	.33	2.38 ±	1.04	.85 ±	.77
Tumor	2.27 ±	1.66	7.44 ±	4.61	12.39 ±	23.69
Liver	1.65 ±	1.06	8.98 ±	2.50	.94 ±	.63
Bone	1.64 ±	.62	2.26 ±	.83	1.09 ±	1.78
Thyroid+	6,910.00 ±	2,991.00	6,900.00 ±	4,035.00	136,158.00 ±	76,537.00
			96 Hours			
Muscle	.17 ±	.08	.67 ±	.60	.44 ±	.11
Blood	.28 ±	.16	.64 ±	.19	.46 ±	.22
Tumor	1.28 ±	1.17	3.98 ±	3.60	1.38 ±	1.35
Liver	.50 ±	.35	3.92 ±	2.51	.77 ±	.51
Bone	.53 ±	.45	1.97 ±	1.10	.99 ±	.37
Thyroid+	6,636.00 ±	2,240.00	6,699.00 ±	1,415.00	140,476.00 ±	63,067.00

‡All values expressed as cpm/mgm wet tissue

*Standard deviation

+cpm contained in the thyroid gland

cline. Table II records the distribution in mice of these radioactive drugs at 24, 48, and 96 hours. It is obvious and statistically significant that the activity in the N-pyrrolidino-methyl-substituted tetracycline remains in the tissues longer, and at a higher concentration in the liver than does the nonamide-substituted tetracycline. This may be caused by a prolonged excretion of the drug.

The tumor in mice appears to take up the radioactive drug preferentially, but again the large standard deviations, due to tumor variability and tumor iodide uptake, render this data insignificant.

We conclude from these studies that the N-amide-substituted tetracyclines are taken up, retained, or both retained and taken up by the liver more than the nonamide-substituted tetracyclines, and that when a "methyl amine" is substituted on the amide group of tetracycline, the drug is preferentially taken up, retained, or both taken up and retained, longer by the liver. N-pyrrolidino-methyl tetracycline concentrates to a higher degree in serum than does tetracycline when each is given intramuscularly (14). The amide-substituted tetracycline in this study also shows this to be true.

The radioactivity present in the liver of a dog, given a high specific activity iodopyrazole tetracycline, was sufficient for obtaining a scintigram between 4 and 24 hours (Fig. 4). When a low specific activity but equal amounts of radioactivity were given, the scintigrams were not well resolved. From this study it is concluded that the liver becomes saturated with the drug and sug-

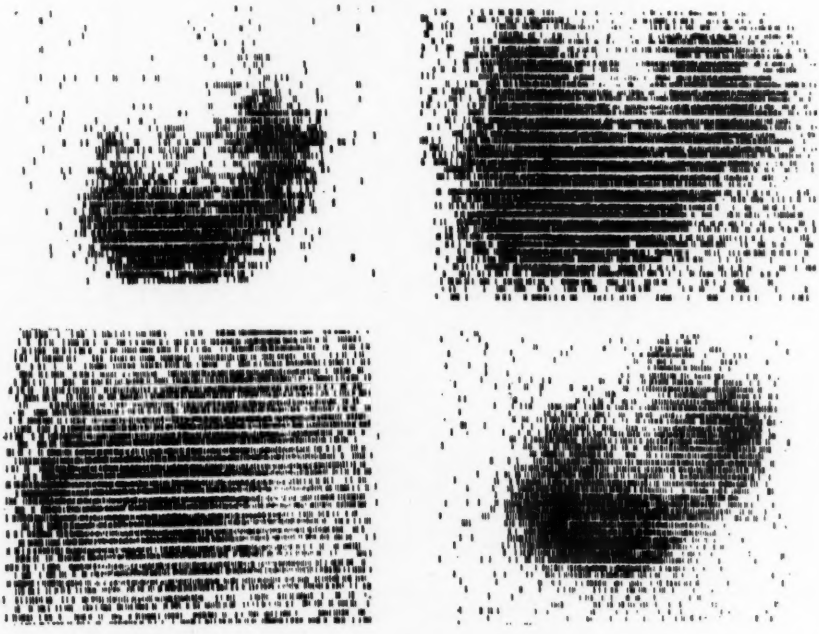

Fig. 4 Scintigrams of 4 dog livers at 4 to 8 hours after a single injection of 10 mg/kg body weight of N-(4-radiodopyrazole-methyl)-tetracycline.

gests that the higher blood levels of the amine substituted tetracycline may be a result of a decreased excretion rate. This is further supported by the study in which sufficient radioactivity remained in the liver of one dog so as to obtain a scintigram 48 hours after the single injection of the radioactive drug (Fig. 5).

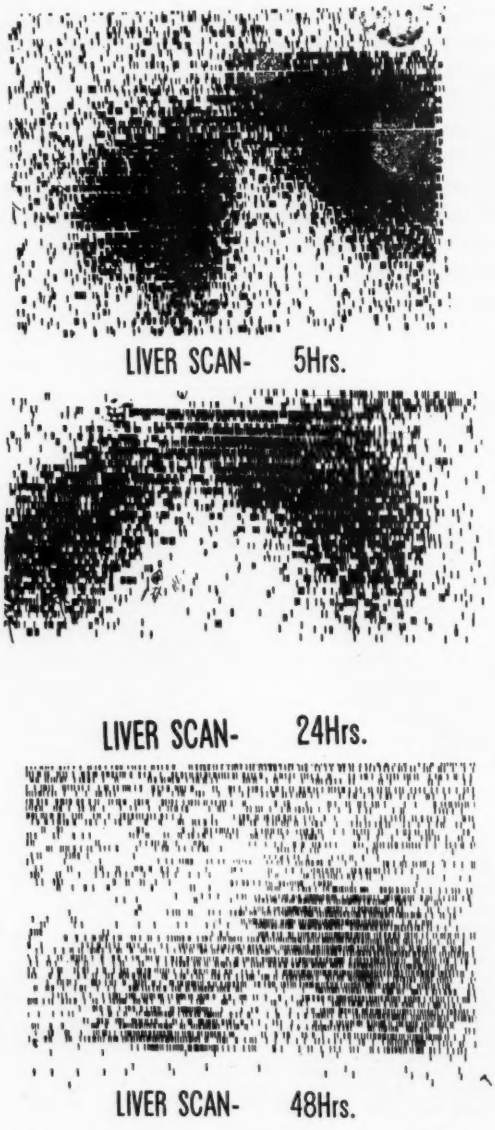

Fig. 5 Scintigrams of a dog liver at 4, 24, and 48 hours after a single injection of 10 mg/kg body weight of N-(4-radioiodopyrazole-methyl)-tetracycline.

A blood turnover study in dogs given 10, 20 and 40 mg of iodopyrazole tetracycline per kg of body weight, demonstrated a biphasic blood disappearance curve, a rapid decline phase, and a more gradual decline "after phase" (Fig. 6). In the dog (Dog #4, Fig. 6) that received, orally, 60 mgm of radioiodopyrazole tetracycline per kg of body weight, the radioactivity in the blood rose and peaked between 12 and 24 hours. Thus, a reabsorption and recycling results, in part, in the gradual decline phase of iodopyrazole tetracycline from the blood.

SUMMARY

An N-(4-radioiodopyrazole-methyl)-tetracycline has been synthesized and its distribution in mice with tumors studied. The radioiodopyrazole tetracycline was found to accumulate in the liver of mice and dogs but not in the tumor of mice. The radioactive drug accumulated sufficiently in the livers of dogs so that it was possible to obtain scintigrams from 4 to 24 hours after the initial injection of the drug. The distribution in mice of 9-radioiodo-6-deoxy-6-demethyl tetracycline and the N-(pyrrolidino-methyl)-9-radioiodo-6-deoxy-6-demethyl tetracycline were compared with the distribution in mice of iodopyrazole tetracycline.

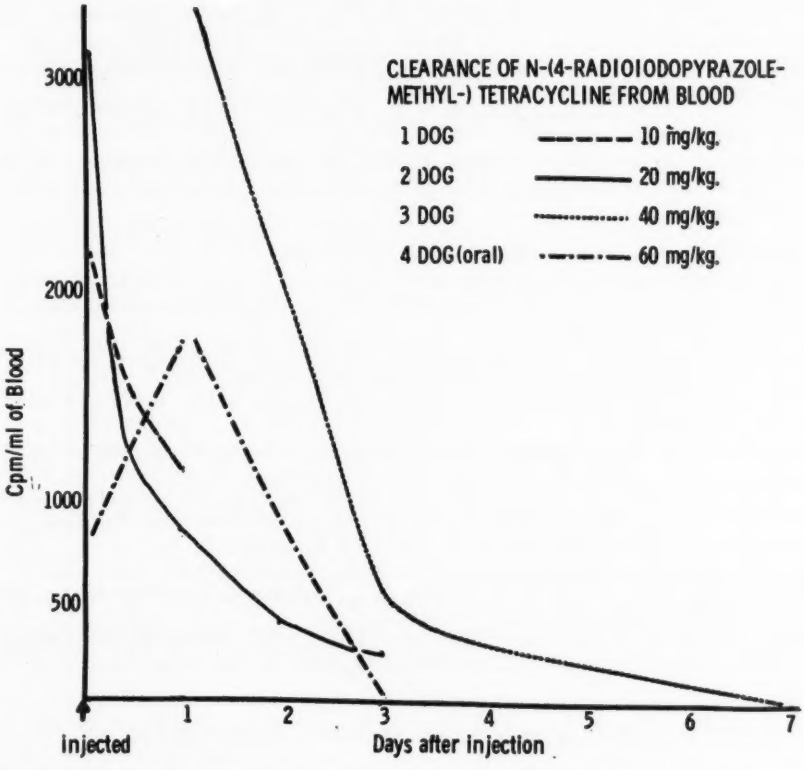

Fig. 6 Clearance of N-(4-radioiodopyrazole-methyl)-tetracycline from blood of dogs.

The N-amide-substituted tetracyclines remained in the liver at higher concentrations than the nonsubstituted tetracycline and concentrated to a higher degree in muscle, femur, liver, tumor and blood of mice than did the nonamide-substituted tetracyclines. It is suggested that N-(4-radioiodopyrazole-methyl)-tetracycline might be used to study liver function.

ACKNOWLEDGEMENTS

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Glucose-1-C-14 Oxidation by Blood: A Potential Test for Tissue Effects of Thyrotoxicosis[1,2]

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INTRODUCTION

To the present, with the exception of the BMR, no simple clinical test has been available to estimate tissue levels of thyroid hormone. It would seem that a test of this type would be clinically useful because thyrotoxicosis can present a symptom complex similar to and easily confused with many other diseases. The routine use of radioisotopic tests has done much to improve our ability to diagnose thyrotoxicosis. Generally these tests measure the ability of the thyroid gland to metabolize iodide or the rate and level at which thyroid hormone is being transferred in the serum. It has been found that these tests show only a fair correlation with clinical severity. They may show an over active thyroidal iodine metabolism and even elevated serum levels of thyroid hormone in euthyroid patients. (1) Some investigators have found that geriatric patients have lower thyroid I-131 uptakes than younger people. (2) This suggests that the daily hormone requirement and production are reduced in geriatric patients. If these individuals have lower euthyroid levels of thyroxine production, they should develop thyrotoxic symptoms and signs at levels of hormone production which might not be abnormal for younger individuals. Other disease states and hormones effect tissue response to thyroid hormone which can obscure the clinical diagnosis of thyrotoxicosis. (3, 4)

With these considerations in mind, we have attempted to find a simple clinical test which could be used to evaluate tissue reaction to thyroid hormone. Certain metabolic changes are thought to be associated with high levels of circulating thyroid hormones. These include creatinuria, increases in serum levels of

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[1]Radioisotope Laboratory, Methodist Hospital and Department of Medicine, Baylor College of Medicine, Houston, Texas.

[2]Partially Supported by NIH Grant #5435.

certain glycolytic enzymes, (6, 7, 8) elevated glycolysis of blood, (9), decreased serum cholesterol, and decreased serum tocopherol. (5) For various reasons, none of these tests has proven practical for routine clinical evaluation of thyroid state. Recently in a study designed to investigate glucose metabolism of blood, especially eryrthocytes, we found that increased thyroid hormone levels suppressed the initial oxidation by the hexose monophosphate shunt pathway as measured by the production of C-14-O_2 from glucose-1-C-14. (8, 10) This suppression was assumed to be due to changes in erythrocyte metabolism although rigorous attempts were not undertaken to determine what portion of this effect was a result of differences in the number and metabolism of leukocytes and platelets or differences in blood sugar. This technic was found to correlate adequately with clinical thyrotoxicosis and its use is suggested to estimate tissue response to hyperthyroidism.

METHOD

Five milliliters of heparinized blood was obtained from normals and patients with the clinical symptoms of thyrotoxicosis. The diagnosis of thyrotoxicosis was by clinical examination, I-131 uptake, radioactive triiodothyronine serum binding test and protein bound iodine.

After a fifteen (15) minute pre-incubation period in a Warburg flask, 0.5 ml of a 1 per cent solution methylene blue and 5 μc of glucose 1-C-14 (0.08 mg/μc) was added. Incubation was continued for 1-3 hours at 37° C in a continuous stream of 100 per cent oxygen. The evolved carbon dioxide was collected by bubbling it into 10 ml of 0.5 M of hyamine hydroxide.[1] The radioactivity present in 1 ml of the hyamine solution was determined by using a liquid scintillation detector. The results are expressed as the percentage of the injected C-14 collected as radioactive carbon dioxide.

For the animal experiments, two hundred gram male rats given an ordinary rat diet were used in these studies. The adrenalectomized rats were given 0.85 per cent saline ad lib as drinking water. The thyroxine treated animals were given 1 mg of sodium-L-thyroxine (T-4) intraperitoneally each day. The thyroid stimulating hormone[2] (TSH) was given subcutaneously. The rats were killed with ether and vena cava blood collected.

RESULTS

Table I shows the results of these studies in rats treated with thyroid and TSH to simulate the thyrotoxic state. It can be noted that 1 mg of T-4 intraperitoneally per day for seven days failed to suppress C-14-O_2 production. However, continued treatment with T-4 for 30 days resulted in a pronounced suppression of glucose oxidation showing that this change does not occur immediately. However, thyroid stimulating hormone produced a marked suppression of this oxidation within seven days. Hypothyroidism produced by surgical thyroidectomy

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[1]Packard Instrument Co., LaGrange, Ill.

[2]Thyrotropar, Armour.

did not cause an increase in C-14-O_2 production. Adrenalectomy produced a partial suppression of this activity but not to levels seen after prolonged thyroid administration.

Table II shows how the treatment of thyrotoxicosis affects glucose oxidation by blood from thyrotoxic patients. The percentage C-14-O_2 production of the thyrotoxic blood is considerably below that of the euthyroid controls and it continued to be less than normal for 12 weeks post treatment. Yet at this time, patients treated for thyrotoxicosis appear clinically euthyroid. The results of these determinations suggest that the metabolic changes produced by the thyrotoxic state continue for at least twelve weeks. Patient number six (6) is of special interest since this patient had been receiving propylthiouracil for three months and when first seen was close to being clinically euthyroid.

Table III shows the effect thyroid state has on the oxidation of glucose made radioactive only at the second carbon. Oxidation of this carbon is not reduced until the third hour of incubation in blood from thyrotoxic individuals. It is the function of the hexose monophosphate shunt pathway to oxidize carbon number one converting glucose into ribulose. Enzymatic pathways are available to reconvert the ribulose carbons into glucose. When this occurs, the second carbon of the original glucose molecule becomes the first carbon of the newly formed glucose. This carbon can now be oxidized by either the hexose monophosphate shunt pathway or the glycolytic pathway.

DISCUSSION

Incubating erythrocytes with methylene blue and glucose, labeled in either the first or second position with Carbon 14, produces radioactive carbon dioxide

TABLE NO. I

EFFECT OF THYROID STATE ON HEXOSEMONOPHOSPHATE SHUNT PATHWAY OXIDATION OF GLUCOSE-1-C-14 BY BLOOD FROM RATS TREATED TO SIMULATE CLINICAL THYROID ABNORMALITIES

Condition	*No. of Animals*	*1st Hour*	*2nd Hour*
		Percent of C-14 Collected as CO_2	
Control	8	10.2 ± 0.5	28.0 ± 0.9
TSH 1 Unit for 7 days	5	5.1 ± 0.5	18.8 ± 0.7
1 mg T-4 for 7 days	5	10.6 ± 0.9	24.5 ± 1.9
1 mg T-4 for 30 days	4	4.5 ± 0.6	
Hypothyroid 21 days	5	9.0 ± 1.0	24.1 ± 0.8
Adrenalectomy + T-4 for 7 days	4	7.6 ± 0.4	24.9 ± 0.9

Mean ± Standard error of mean. Each incubation consisted of 5 ml heperanized blood, 5 μc glucose-1-C-14 and 0.5 ml of 1% methylene blue.

only as a result of glucose oxidation by the hexose monophosphate shunt pathway. (11) Other cells, including leukocytes produce carbon dioxide from glucose oxidation by the Krebs cycle as well as the hexose monophosphate shunt pathway. Thus, only in erythrocytes is it possible to assure separate of these two pathways by the collection of carbon dioxide. Radioactive sugars are necessary for these determinations because the volume of carbon dioxide released is small and difficult to measure by non radioactive methods. In addition, the specifically labeled sugars effectively dilute the small amount of carbon dioxide released by the Krebs cycle contained in leukocytes. The mean percentage of carbon dioxide produced by the normal blood is quite close to the values obtained by others who washed the erythrocytes to remove the leukocytes prior to incubation. (12) Because of this, it is assumed that the difference noted between thyrotoxic and normal blood is a result of changes in erythrocyte metabolism rather than changes in the number of leukocytes.

Thyroid feeding of rats produced a decrease in the C-14-O_2 produced from glucose-1-C-14. This effect did not occur immediately suggesting that contraregulatory mechanisms do not fail immediately. It is possible also, that there is a delay between injection and the time when the thyroid hormone becomes active in metabolism. Previous work has shown that acute administration of 100 ugms of triiodothyronine to normal subjects resulted in partial suppression of this oxidative pathway in two days. (10) However, partial suppression can be produced also, by acute variations in cortisone levels. The response to TSH occurred within one week, showing that endogenous thyroid hormone may be different from thyroxine or that the effects noted may be partially related to other metabolic activities of this preparation of thyroid stimulating hormone.

TABLE NO. II

INCREASE IN PERCENTAGE C-14 O_2 PRODUCED BY BLOOD FOLLOWING TREATMENT OF THYROTOXICOSIS WITH RADIOACTIVE IODINE

Post Treatment	*Week* 0	6	12	*Week* 0	6	12
Duration of Incubation	1 Hour			3 Hour		
Thyrotoxic Subjects						
1	4.8	6.1	8.2	26	30	30
2	4.4	6.6	—	27	27	—
3	4.6	6.7	8.4	27	30	—
4	5.3	7.1	—	—	—	—
5	2.0	4.0	—	—	18	—
6	8.9	7.8	7.1	37	31	29
Mean of 12 Normals	10 ± 0.4			40 ± 2		

Percentage C-14 O_2 produced from 5 μc of glucose-1-C-14.

It has previously been demonstrated that thyrotoxic blood shows depression of HMP shunt pathway. (8, 10) That this is not permanent in patients with the clinical diagnosis of thyrotoxicosis is shown by the return to normal of the values following treatment of this disease. Prolonged treatment of a thyrotoxic patient with propylthiouracil, as one might expect, corrected the depression of this oxidative pathway.

The demonstration of a slight depression in glucose oxidation when the second carbon is made radioactive suggests that thiamine deficiency does not participate in these changes. (11) It has been shown, using conditions similar to those used here, that a thiamine deficiency markedly reduced the recycling of carbon by the hexose monophosphate shunt pathway, but did not suppress oxidation by glucose-1-C-14. If a vitamin deficiency were a part of this phenomenon, then we might expect the changes to be delayed since erythrocytes of rats fed a thiamine deficient diet do not show depressed transketolation until after the 12th day of treatment. An alternate explanation could be that the glucose-2-C-14 oxidation was a result of oxidation in the Krebs cycle by leukocytes. Since thyrotoxic blood oxidizes glucose-1-C-14 more slowly than normal blood, we would expect less ribulose to be available for reconversion into glucose. The depressed oxidation of the second carbon during the third hour of incubation would be consistent with this. The failure of the oxidation to increase in the third hour might be then, a manifestation of the depressed HMP.

The conditions used in these experiments stimulate oxidation by the hexose monophosphate shunt pathway. (11) This occurs whenever methylene blue is added to blood. This is obviously an artificial situation and caution should be exercised before drawing any conclusions about metabolic processes in normals and thyrotoxics from these studies.

TABLE NO. III

PERCENTAGE OF C-14 O_2 PRODUCED FROM GLUCOSE-2-C-14 BY BLOOD OF NORMALS AND THYROTOXIC PATIENTS

Hour of Incubation	*0-1*	*1-2*	*2-3*	*0-3*
Four Normals	1.3 ± 0.6	1.4 ± 0.2	2.5 ± 0.1	5.3 ± 0.2
Thyrotoxic Patients				
1	1.2	0.8	1.4	3.4
2	1.4	1 5	1 3	4.3
3	1.5	—	—	—
4	1.0	1.3	—	—
5	1.4	1.8	0.8	4.0
6	0.6	1.2	1.5	3.3
Mean	1.2	1.3	1.2	3.8

Mean ± Standard Error of mean.

SUMMARY

1. Blood from thyrotoxic patients oxidize glucose-1-C-14 and glucose-2-C-14 at a slower rate than does blood from normals.

2. Animal experiments have shown that similar changes can be produced by administration of thyroxine and thyroid stimulating hormone.

3. This depression of glucose oxidation tends toward normal as clinical thyrotoxicosis subsides.

4. This procedure has been suggested as an in vitro method for estimating tissue levels of thyroid hormone activity.

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JOURNAL OF NUCLEAR MEDICINE 4:399-403, 1963

Supplementing the Rate Meter by Adding an Efficient Low-Pass Filter[1]

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The function of a rate meter is to produce an average voltage positively related to pulse repetition rate. The randomly occurring pulses emerging from nuclear detection equipment exceeding a certain amplitude usually trigger a one-shot multivibrator stage and the standardized pulses emerging from this multivibrator are integrated by a simple capacitor. The decay characteristics of this capacitor and its associated circuitry are commonly expressed in terms of its time constant. When a study is undertaken in which a change in count rate is observed, the rapidity of this change is considered and a time constant chosen which will follow the changing count rate with reasonable faithfulness. A time constant shorter than necessary is avoided since it is generally recognized that more high frequency noise will appear superimposed on the desired curve.

When considered in this way simple capacitance integration seems quite straightforward.

However, if the count rate is thought of not in terms of rapidity of change but inversely in terms of frequency content of the desired variable and frequency distribution of unwanted noise, the simple capacitance integrator seems quite inefficient by modern electronics standards. Its ability to reject noise at nearly the same frequency as the signal is very poor.

A train of random pulses has in it information throughout a very broad frequency spectrum. As the pulse rate becomes high and the pulse duration short, the noise distribution approaches "white" noise; *i.e.*, the signal is distributed uniformly throughout the entire frequency spectrum.

The capacitor connected between the pulse and ground can be thought of as a frequency-selective device attenuating higher frequencies. The extent of this attenuation becomes greater with rising frequency such that each time the frequency is doubled the signal is attenuated twice as much (see curve B, Fig. 1). In other terms we can state the single capacitor discriminates against the power content of higher frequencies at a rate of 6 decibels per octave.

If there is some sinusoidal increase and decrease of count rate at a particular frequency, the frequency content of the signal is no longer uniform but

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contains an excess of energy at this frequency. If we wish to display this cyclic sinusoidal change in count rate we ideally should like to display only the frequency content up to that frequency, with exclusion of the noise content of the signal at higher frequencies. If a simple capacitor is chosen which will, in its particular circuit configuration, attenuate this signal frequency very little then noise at twice this frequency will, under the best conditions, be attenuated only 6 decibels and at four times this frequency only 12 decibels. At sixteen times the desired frequency the noise will still be attenuated only 24 decibels (see curve B, Fig. 1).

From this it would seem that a considerable improvement in noise rejection should be possible if the attenuation increased more steeply above the desired signal frequency.

This is a very general problem in electronics. When information is contained in a particular range of frequencies a system is designed which will pass this range and sharply attenuate all other frequencies. This situation is very similar to that encountered in phonographs reproducing older shellac records. Early recording equipment did not record sound frequencies higher than about 6,000 CPS. Since the recording material itself contained microscopic particles of

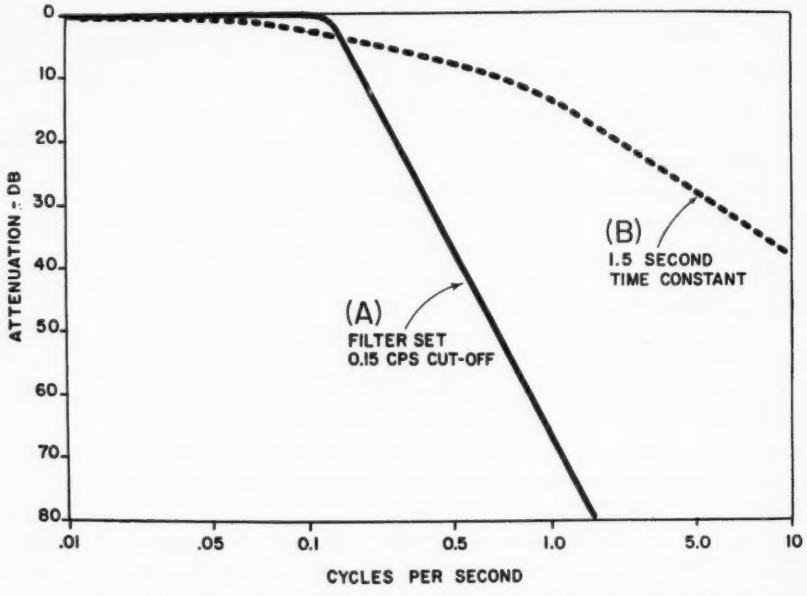

Fig. 1. Showing the attenuation of a signal as a function of frequency as produced by the commerical low-pass filter (A) and a single capacitor integrator (B). The cut-off frequency of the filter has been set at 0.15 cycles per second. The simple low-pass filter effect of the simple integrator has a time constant of 1.5 seconds. Note that the low-pass filter will better preserve a desired signal at 0.1 cycles per second relative to an unwanted signal at a higher frequency such as one cycle per second. Any harmonic content in this 0.1 CPS signal will, of course, be attenuated tending to reduce the shape of such signals just below the cut-off frequency to a sinusoidal curve.

irregular size and position the record itself superimposed a relatively "white" noise heard as a "hiss" on the recorded sounds. Since much of this occurred at frequencies higher than 6,000 CPS but within the audible range it could be removed with a reduction of audible noise but with no loss of music harmonic content. Usually a simple "scratch filter" was employed. The circuitry used was that of a simple resistance-capacitance low-pass filter as used in a simple rate meter. When confronted with this same problem audio engineers seeking the utmost in signal to noise ratio commonly use a sharp cut-off filter as proposed for rate meters in this article. By setting its cut-off frequency at the highest frequency to be preserved, higher frequencies can be more sharply attenuated. This is all predicated, of course, on a knowledge of the frequency content of the desired signal.

When a noisy tracing is obtained from a rate meter and we "eyeball" a curve through what seems to be a mean path through the noise, we are actually performing a frequency discrimination mentally trying to preserve the low-frequency component and ignoring (attenuating) the higher frequencies. This is, of course, very prone to subjective interpretation. It would seem more desirable to follow the low-frequency trends by a coldly objective piece of hardware. Ideally all of the original pulses would be recorded on magnetic tape and later subjected to autocorrelation. Here the low-frequency trend can be recovered with extreme rejection of high frequency components. The equipment, however, is very elaborate and the curve does not appear as the event happens.

The inefficiency of the simple resistance-capacitance network as a frequency discriminator is well known and such filtering is seldom relied upon except for the most simple of applications or where the signal and noise differ greatly in frequency.

In considering the nuclear rate meter, then, it would seem more practical to consider the frequency content of the signal which must be displayed and design a circuit which will cut off sharply all higher frequencies.

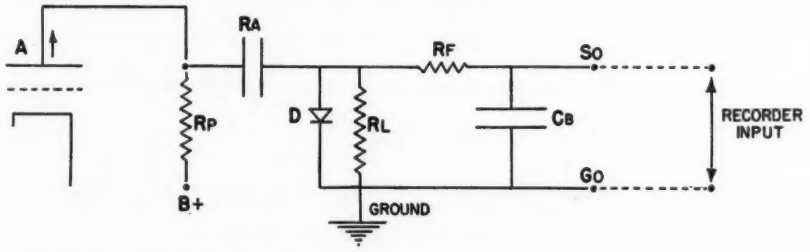

Fig. 2. In this output section of a rate meter circuit A represents one half of a multivibrator stage. When this tube conducts during a pulse the voltage on its plate drops due to plate resistor RP and a negative pulse is conducted to the top of resistor RL by capacitor CA. This pulse is clamped negative by diode D. Through resistor RF, capacitor CB develops a charge which appears across SO and GO as the rate meter output voltage. Capacitor CB will discriminate against higher frequency components at a rate of 6 decibels per octave. The cut-off frequency will be determined by the values of RF and CB. In our apparatus the low-pass filter was introduced between SO and GO and the recorder input.

Commercial low-pass filters are available for this purpose and can be connected between rate meter output and recorder as carried out in the application described here.[1] An advantage of the particular filter we have used is its ability to pass the D-C component of the rate meter output. Another approach to application of the low-pass filter in biological work has been described by White. (1)

APPLICATION

In our particular application we had a biphasic wave of the configuration of the thicker line of Figure 3. This is the first derivative of a rate meter output defining a bolus of isotope passing through the brain blood pool. (2) This curve indicates the rate of change of cranial isotope content and is inherently much noisier than its parent curve (the rate meter output). However, this entire discussion is equally applicable to direct rate meter output. We estimated that the positive portion of the curve approximated one half of a sine wave with a frequency of about 0.1 cycles per second since the positive half of this sine wave lasted approximately 5 seconds. The negative phase is of a somewhat lower frequency, approximating 0.06 cycles per second.

From this it would seem unnecessary for our system to display information at frequencies higher than 0.1 cycles per second; the frequency of the positive half of the curve.

In Figure 3 the same pulses have been fed to two identical rate meters. The thinner line is a direct recording of a rate meter having a standard 1.5 second

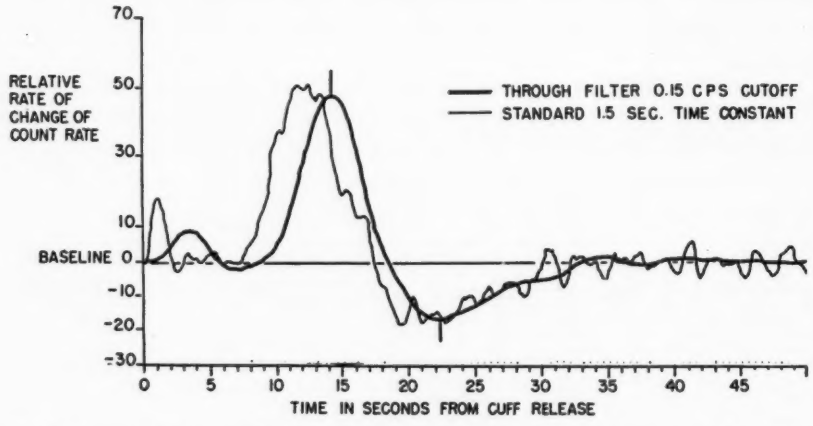

Fig. 3. Comparing a standard rate meter having a single capacitor integrator of 1.5 seconds time constant with the same signal passed through a commercial sharp cut-off low-pass filter set at 0.15 cycles per second cut off. The delay in the filtered signal is inevitable but does not alter the relationships between different parts of the curve since the delay is fixed and depends upon the cut off frequency at which the filter is set. The information desired was the time of occurrence of the positive and negative peaks as marked on this illustration.

[1]Our filter was purchased from Spectrum Instruments, Inc., Long Island City 3, New York.

time constant. The thicker line indicates the output of another rate meter with a 0.3 second time constant but after passage through the low-pass filter set at a 0.15 cycles per second cut-off.

It can be seen that the filtered curve lags about three seconds behind the unfiltered. This is a fixed and unavoidable time delay introduced by the filter. Since the entire tracing is displaced by the same amount it retains all time relationships within the tracing.

The early, sharp peak appearing at zero to two seconds is of too high a frequency to be passed undistorted by the filter and is attenuated. This peak apparently represents Compton scatter from the deposition into the thorax of an antecubitally injected bolus of radioisotope. Since it is of little value it is unimportant if it is distorted by the filter. If we were to raise the cut off frequency to perhaps 0.3 cycles per second this early peak could probably be preserved, but at the sacrifice of the later signal in which we are interested.

The data we wished was the time interval from the positive to the negative peaks. It is obvious that this measurement is prone to much less subjective interpretation in the filtered curve.

Some distortion is introduced into these filtered curves by the less-than-critical damping inherent in extremely sharp cut-off filters. It would probably be more desirable to have a critically damped system. Such a system could easily be built into the integrator section of the rate meter.

SUMMARY

1. In those applications where the frequency content of a desired variable is known, the incorporation of a sharp cut-off, low-pass filter between rate meter and recorder is capable of improving the signal to noise ratio of a standard rate meter in which a single capacitor is used as an integrator. The highest frequency content of interest in the signal is estimated, and the filter cut off is set somewhat above this. One application in defining curve peaks is described.

2. Curve-smoothing by this means is relatively objective.

3. A reduction of isotope dosage is possible.

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The Quantitative Radiorenogram for Total and Differential Renal Blood Flow Measurements[1,2]

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INTRODUCTION

The radioisotope renogram was devised originally (1) to measure individual kidney function, externally, without the hazards of ureteral catheterization. It has largely accomplished this purpose in spite of the original empirical terminology and description of its three segments (vascular, tubular and excretion (1)) and the all too common technical error of inaccurate kidney localization. This paper is presented to show how the radiohippuran renogram as currently performed and interpreted by the authors (2-6) can give numerical values of total and individual renal blood flow.

CURRENT RENOGRAM INTERPRETATION

The height of the first segment now called "tracer appearance" is no longer considered a useful *index* of renal vascular capacity or volume of the renal vascular bed, because extrarenal factors dominate this phase (3,4). The slope of the second segment (now called "blood flow") is not an indicator of tubular cell function as originally presumed (1). It is an index of *relative renal blood flow* for the following reasons: (1) Microgram to milligram amounts of hippuran (ortho iodo hippurate) which give plasma concentrations below 10 mg per cent, are removed from the blood by the normal kidney with high efficiency (92%) during each passage through the organ (7). (2) Nearly all of the hippuran which is extracted *remains in the kidney* during the entire second phase of the renogram (2, 4, 5, 6). (3) This concept is based on the same tubular transport and filtration mechanisms as the classical clearance method of Homer Smith (7).

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(4) Renal artery constriction in dogs and rabbits, which reduces blood flow as measured by an electromagnetic flow meter or by collection of blood flowing directly from the renal vein, likewise depresses the slope of the renogram's second segment. (5) Finally, the slope of the renogram's second segment is found to be a reliable indicator of renal ischemia in hypertensive patients with proved renal artery occlusive disease (3, 4, 5, 6, 8, 9, 10).

The third segment (drainage) registers the rate of tracer discharge from the kidney. In the absence of obstruction in the upper urinary tract, the drainage segment declines as rapidly during the first few minutes as its blood flow counterpart has ascended. Thereafter, it falls more slowly in nearly parallel relation with the rate of tracer disappearance from the blood. If tracer did not leave the kidneys, the only information one could derive from the renogram would be *relative blood flow* to the kidneys. However, urine is made continuously; hippuran becomes part of that urine and is discharged from the kidney. As a result, the renogram also indicates the freedom with which urine is discharged from each kidney.

During these investigations (4, 5) the *fallacy* of another original renogram concept was disclosed, namely, "the time to reach maximum renal radioactivity represents a transient equilibrium between the rates of tracer accumulation and discharge from the kidney." The equilibrium concept is incorrect because *it implies that tracer leaves the kidney before* the peak level is reached, when in fact *tracer is almost completely retained* in the kidney for the entire duration of the second segment. Also, the time of tracer discharge from the kidney coincides with its first entry into the bladder a few seconds later. The time at which these two events occur *after* tracer injection is a measure of *renal transit time,* a new and important parameter of the renogram.

Transit time is dependent only on the rate of urine flow from the kidney (3). Fluid restriction or antidiuretic hormone injection prolongs the time which radiohippuran spends in the kidney, by reducing the rate of urine flow (4). Prolongation of transit time is found in severe renal ischemia (3, 4, 5, 6). In unilateral renal vascular disease it is caused by a reduced volume of filtrate and to excessive water reabsorption in the tubules with consequent decrease in the rate of urine flow from the ischemic kidney (4).

EQUIPMENT

Two matched scintillation detectors each collimated to view the entire kidney and a minimum of surrounding tissue are required. They are connected through ratemeters to rectilinear recorders. Each channel must be adjustable to respond equally to a given source under identical geometric conditions. The detectors should be collimated to view a circular area 12.5 cms diameter at the center of the kidney, 4-5 cms beneath the flanks. The optimum test dose of radiohippuran is the amount in μc which gives minimal statistical variation in the tracings when the ratemeters are operated with a short time constant (2-5 seconds).

TECHNIQUE

The renogram should be performed routinely with the patient in a comfortable sitting position even though similar tracings are produced with the patient lying prone or supine (11, 12). The upright position is preferred so that nephroptosis may be detected and the possibility of orthostatic hypertension discovered on the first examination. In hypertensive (4, 5, 6) and/or pyelonephritic patients (2), the test should be run first following 12-18 hours of fluid restriction and repeated 2-4 hours later, after giving 1 litter of water. Examination during the hydropenic state, increases the probability of detecting significant differences in blood and urine flow between kidneys and accentuates abnormalities of urine drainage (2).

KIDNEY LOCALIZATION

To obtain renograms suitable for quantitative analysis, each probe must view the entire kidney. Exact placement over the renal areas is best obtained by the tracer method using Hg^{203} or ^{197} chlormerodrin. Thirty minutes after intravenous injection of 2-3 μc, relatively constant renal radioactivity levels are reached in association with low tissue background (5, 6). Unlimited time is permitted thereafter, to determine the sites of maximum radioactivity. The slow excretion of Hg tracer does not invalidate subsequent measurement of radiohippuran excretion following the renogram, provided the test dose of hippuran exceeds the Hg localizing dose by a factor of 10 and/or the urine radioactivity is measured with pulse height discrimination.

DIFFERENTIAL RENAL PLASMA FLOW MEASUREMENT

The slopes of the renogram's second segments are indices of relative renal plasma or blood flow. They may be determined by drawing the best tangent or

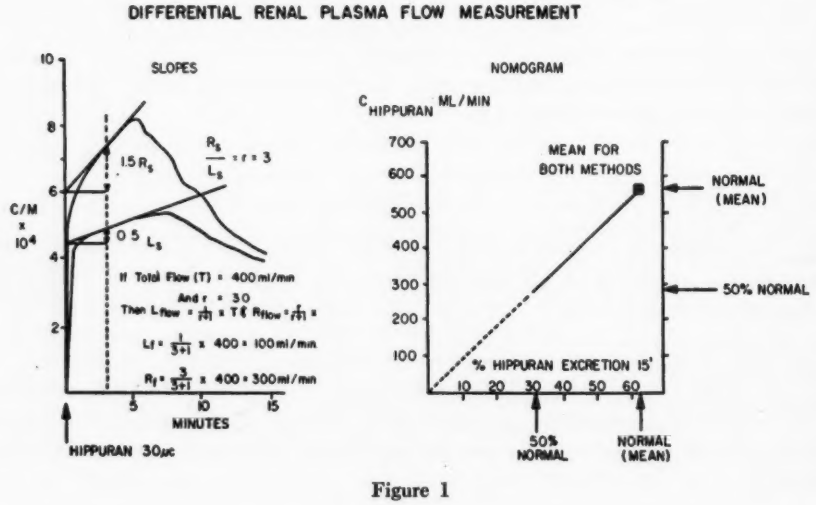

Figure 1

secant through each curve at the same point or points in time, following tracer injection. In the illustration (Fig. 1) the slopes of the right and left second segment curves are determined from their tangents at 3 minutes. The ratio, r, of the slopes of the right and left kidneys R_s/L_s, equals 3.0. Thus, the proportion of blood flowing to the right versus the left kidney is 3:1.

Numerical values for individual flow can then be determined provided one knows the flow to both kidneys or total flow (T_f). T_f or effective renal plasma flow is measured accurately by the clearance of radiohippuran (Chipp I^{131}) (corrected to surface area of 1.73 m^2) and *percent excretion of radiohippuran in 15 minutes* as presented in the nomogram (Fig. 1). The solid line in the upper half of the range is based on clearance vs. excretion tests in 12 normal subjects and on similar examinations in 44 patients with renal disease. The dotted line indicates that the same relation does not hold throughout the lower half at least on the basis of the limited information now available. Therefore until further clearance and excretion values are obtained from patients with advanced renal disease, the nomogram is valid for converting percent excretion to total flow in ml/min *only* within the range exceeding 30 per cent excretion and 280 ml/min clearance. Fortunately, patients with unilateral renal disease seldom have excretion and/or clearance values below 50 per cent of normal.

DISCUSSION

The radiohippuran renogram can give quantitative information on *differential* renal blood flow, provided it is performed properly and one knows a value for total flow from either the radiohippuran clearance or its percent excretion in 15 minutes (3, 4, 5, 6, 14). The important factors in its performance, include matched detector-recorder systems, optimal collimation and exact kidney localization. These three major requirements must be met by the means previously described. In addition a third probe-ratemeter-recorder system (cystogram) is desirable but not essential. The cystogram helps distinguish artefacts from abnormalities in the renal tracings, confirms the measurement of renal transit time and gives a visual record of total excretion and urine drainage rate (2). Also, the third probe is useful for detecting possible urinary retention and/or the completeness of the 15 minute urine specimen needed for accurate determination of percent radiohippuran excretion as a measure of total renal plasma flow.

The work of Tauxe *et al* (15) stresses the need for a standardized renogram technique to permit numerical analysis of individual tracings in comparison with the norm. Previous quantitative methods of renogram analysis were based on misinterpretation of the curves and did not provide measurements of individual renal blood or plasma flow (16, 17, 18). The proposed *quantitative* method should extend the use and value of the renogram in the future, particularly in the problem of renal hypertension. It is a far more reliable screening method than the Howard test (8) or any differential function or clearance procedure, which requires ureteral catherization. Leakage around catheters and other technical factors invalidate the results of such methods at least 15-20 per cent of the time even in experienced hands (8a). Furthermore, when urine is collected from in-

dwelling ureteral catheters, the kidneys cannot possibly function normally. Urine drainage is impaired mechanically and possibly by reflex action from ureteral irritation. With proper performance, the renogram can provide more accurate data on renal ischemia and with no trauma or other hazard to the patient. With the severe ischemia required to produce renal hypertension (8), it is extremely unlikely that the renogram would fail as a screening test.

There are three conditions which make quantitative renogram analysis impossible or at least difficult, namely, advanced renal disease (18), edematous states (4) and pelvic location of one kidney. In the first, hippuran is excreted in excessive amounts by the biliary route and in the second its volume of distribution is greatly expanded. These factors plus the added possibility of impaired renal extraction efficiency invalidate both the hippuran clearance and its excretion values as reliable indicators of renal blood flow. Severe ptosis of one kidney or severe skeletal deformity of the pelvis and/or lumbar spine can give renal tracings which are difficult to quantitate, because of unequal distances and thicknesses of tissue between the kidneys and their detectors. Finally, it should be stressed that quantitative renogram analysis depends on exact kidney localization plus symmetrical anatomic and geometric conditions.

Blood flow as measured indirectly by the quantitative renogram remains to be correlated with exact measurements made at operation with electromagnetic flowmeters (19). The accumulation of this information is a major objective of our continuing investigations.

SUMMARY AND CONCLUSIONS

A new method is described for obtaining *quantitative* measurements of total and differential renal blood flow from the renogram plus the percent urinary excretion of radiohippuran. The combined procedure is called the "quantitative radiorenogram." This quantitative procedure should soon replace all other differential function and/or clearance methods which require ureteral catheterization. It detects unilateral renal ischemia with complete safety, relative technical simplicity and better accuracy. The tracer test may be repeated whenever necessary without the inconvenience, discomfort and hazards of ureteral catherization and the expense of anesthesia, radiography, biochemical examinations and hospitalization.

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JOURNAL OF NUCLEAR MEDICINE 4:410-412, 1963

A Study of the Stability of Neohydrin (3-Acetoxymercuri-2-Methoxypropylurea) Labeled With Mercury-203

Leopoldo J. Anghileri, Ph.D.[1]

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INTRODUCTION

The stability of Neohydrin (3-acetoxymercuri-2-methoxypropylurea) labeled with mercury-203 has been studied making use of chromatographic analytical procedures. The radioactive form of this mercurial diuretic is now being intensively used for the detection and localization of brain tumors (1, 2, 3).

In order to study the stability of Neohydrin Hg-203, it was necessary to develop a convenient procedure capable of resolving Hg-203 labeled Neohydrin from its possible radioactive impurity or product of decomposition, divalent ionic mercury (Hg^{++}).

The studies demonstrate the stability of Neohydrin Hg-203 in dilute basic solution. Chromatographic evidence seems to indicate that at a pH of 7.4 Neohydrin in solution exists in two chemical forms, both of which exhibit the same biological behavior.

EXPERIMENTAL PROCEDURES AND RESULTS

Neohydrin Hg-203 was prepared according to the procedure of Rowland, Perry, Foreman and Friedman (4) and dissolved in a solution of 0.05 N NaOH. The Neohydrin Hg-203 in solution initially possessed a specific activity of 46.5 μc/mg in a concentration of 44.4 mg/ml. The solution was stored at room temperature and analyzed at intervals up to 60 days by the procedure described below.

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[1]Volk Radiochemical Company.

TABLE I

CHROMATOGRAPHIC RADIOACTIVITY DATA FROM NEOHYDRIN-HG-203 (IN 0.05 N NAOH)

Time After Preparation	*Free Mercury*	*First Peak* R_f	*First Peak* % *Total Activity*	*Second Peak* R_f	*Second Peak* % *Total Activity*
1 hour	——	0.85	66	0.56	34
1 week	——	0.80	65	0.56	35
2 weeks	——	0.80	60	0.58	40
1 month	——	0.83	64	0.56	36
2 months	——	0.82	51	0.54	49

The solvent used for chromatographic development was ethanol-phosphate buffer, pH 7.4 (1:1). Employing ascending chromatography, Neohydrin Hg-203 was resolved into two substantially equal peaks, the first possessing R_f 0.82 to 0.88 and the second possessing R_f 0.50 to 0.58. Under the same analytical conditions, the R_f of free Hg^{++} is 0.04.

The pH of the developing solvent radically affected the results obtained. At higher or lower pH's, only one Neohydrin Hg-203 peak could be observed. The addition of 2 per cent acetic acid to the solvent (final pH 4.4) resulted in a single peak for Neohydrin of R_f 0.85. Ionic Hg^{++} migrated with an R_f of 0.82. Adding 2 ml of 20 per cent NaOH per 100 ml of buffered solvent (final pH

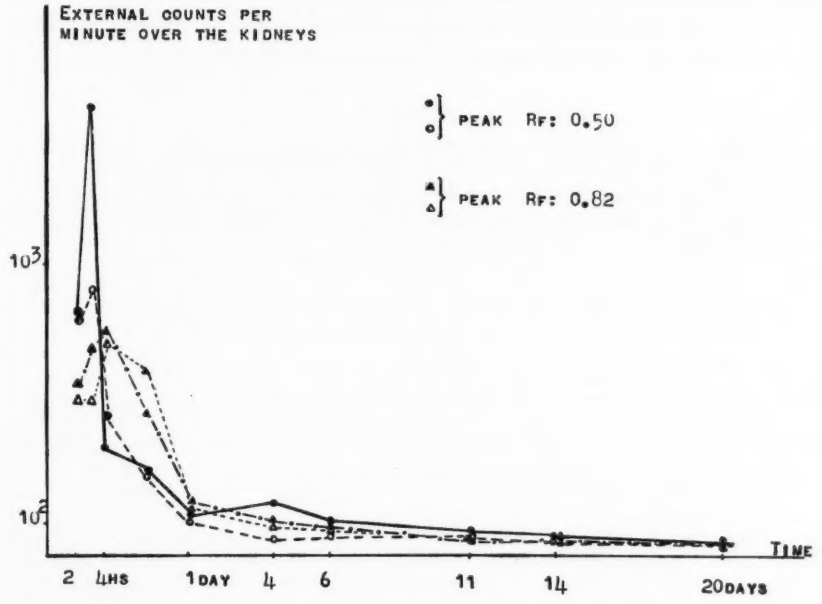

Fig. 1.—Kidney counts after intravenous injection of fractions of Neohydrin Hg-203 (10 μc/kg) in Rabbits.

12.6) resulted in a single Neohydrin Peak with an R_f of 0.60. Hg^{++} remained at the origin under these conditions.

The experiments summarized in Table I indicate the absence of ionic mercury in the product in tests extending up to two months from the time of preparation. The respective R_f's of the two peaks observed under the chromatographic conditions employed, as well as the relative percentages of total Neohydrin Hg-203 activity found present in each of the peaks, are also indicated. Chromatographic studies employing "cold" Neohydrin gave similar results.

The two "Neohydrin Hg-203" peaks separated by chromatography using buffered 50 per cent ethanol were further investigated. The two materials were separately extracted from the filter paper using 0.05 N NaOH and injected intravenously via the marginal ear vein as 10 μc/kg dosages to two groups of rabbits. The rate of disappearance of activity over the renal zone was followed for a period of twenty days using a scintillation counter. The results obtained are illustrated in Figure 1.

DISCUSSION

Neohydrin labeled with Hg-203 in the dilute basic solution exhibits excellent stability for periods up to 60 days.

It is possible that the two peaks separable on chromatographing Neohydrin Hg-203 with buffered 50 per cent ethanol are due to an equilibrium between an anhydro form of Neohydrin, $HN{=}C(O)\text{-}\overline{NH\text{-}CH_2\text{-}CH\text{-}(OCH_3)\text{-}CH_2Hg}$, and the product as normally depicted, $H_2N\text{-}CO\text{-}NH\text{-}CH_2\text{-}CH\text{-}(OCH_3)\text{-}CH_2HgOH$.

The biological behavior of the two forms as evidenced by the rate of elimination on intravenous administration to rabbits is essentially the same.

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CURRENT ABSTRACTS IN NUCLEAR MEDICINE

RADIOACTIVE LYMPHANGIOGRAPHY AS A THERAPEUTIC ADJUNCT.

SEITZMAN, D. M., WHITE, R., HALABY, F. A., AND FREEMAN, J. H., *Am. J. Roentgenology, Radium Therapy* and *Nuclear Medicine* **89**:140, (Jan) 1963

The authors administered 4-24 mc of I^{131}-ethiodol in 2-12 ml of stable ethiodol via intralymphatic cannulae placed in the feet in order to study the feasibility of destroying lymph nodes in the iliac and periaortic chains in patients with tumors which commonly metastasize to these nodes. Because the ethiodol will not be homogenously deposited in a lymph node completely replaced by tumor, only those patients with relatively normal retroperitoneal lymph nodes were selected. In order to avoid excessive amounts of ethiodol reaching the lungs, fluoroscopic localization of the drug is performed during the procedure, and the injection is terminated whenever ethiodol reaches the thoracic duct. Some patients received Lugol's solution to reduce thyroidal I^{131} uptake. At post-mortem examination, the nodes and representative tissue from lungs, liver, kidneys, and spleen were measured for radioactivity. Significant activity was found only in lymph nodes. The beta rad dose was calculated to vary from 1,500 to 15,000 beta rads, and histologic effects on the nodes varied from none to total destruction. No complications or adverse side effects were encountered. It is not clear how many patients have been studied. The authors propose this technique may be applicable especially in tumors of the penis and testis, squamous cell carcinoma of the cervix, abdominal lymphomas, or any other malignancy metastasizing to the inguinal or retroperitoneal nodes.

Inasmuch as ethiodol may fail to penetrate large tumorous nodes and may be shunted to the lungs in patients with blocked lymphatic channels, it appears to the reviewer that the usefulness of I^{131} ethiodol therapeutically may be limited to patients without gross lymph node involvement or to those patients subjected to a prior lymph node dissection.

Abstracted by Joseph P. Kriss, M.D., Stanford Medical College, Palo Alto, Calif.

LOCAL MYOCARDIAL BLOOD FLOW AS INDICATED BY THE DISAPPEARANCE OF NA I-131 FROM THE HEART MUSCLE: STUDIES AT REST, DURING EXERCISE AND FOLLOWING NITRITE ADMINISTRATION.

W. HOLLANDER, I. M. MADOFF AND A. V. CHOBANIAN *J. Pharmacology and Experimental Therapeutics:* **139**:53, 1963.

In dogs, injection of iodide–I-131 directly into the heart muscle is followed by rapid exponential removal with a disappearance half-time of 45 seconds (range 30-60 seconds). Following the rapid decline of radioactivity over the injection site there was a slower rate of disappearance which was similar over both the injected and uninjected portions of the heart and great vessels. Mechanical total occlusion of the anterior descending branch of the left coronary artery resulted in retention of radioactivity at the injection site. Release of occlusion led to disappearance half-times 3-4.5 times that of controls, presumably due to myocardial reactive hyperemia, when the arterial blood supply was only partially occluded, the disappearance rates were only 1/2 to 1/6 that observed in controls. Release of occlusion again resulted in rapid clearance, about twice that observed in control animals.

This technique was applied to 5 patients without clinical evidence of coronary artery disease during open thoracostomy. $T\frac{1}{2}$ iodide disappearance values averaged 1.4 minutes

(range, 1.0-1.8 minute). In 3 patients with coronary artery disease T½ disappearance values of 10.0; 4.5 and 5.5 minutes were obtained initially with values of 9.5; 8.0 and 3.3 minutes obtained when the study was repeated.

In patients with angina pectoris, percutaneous injection of radioiodide into the myocardium gave T½ values of 4-12 (average 8.8 minutes) minutes. Following exercise, the T½ values were reduced to 4.6 minutes average.

Administration of nitroglycerine (0.4 mg, sublengual) did not result in increased clearance as was observed following exercise. The authors suggest the observed results may be due to concomitant reductions in blood pressure caused by the drug.

Abstracted by Paul Numerof, Sc.D., Squibb Institute for Medical Research, New Brunswick, N.J.

Mark Your Calendar Now!

11th Annual Meeting
The Society of Nuclear Medicine

San Francisco Bay Area—Claremont Hotel
Berkeley, California—June 17-20, 1964

President's Message

THAD P. SEARS

The Society of Nuclear Medicine is very active as a national organization. Its membership roster is rapidly growing. Its breadth of interests is widening and its annual meetings are increasingly productive and well attended.

The national Society is administratively composed of its 13 regional Chapters. Some of these came in after the national organization had been founded but it will be remembered that the Society had its origins in the union of several local groups that had simultaneously arisen in various areas of America. In this pooling of interests, the local societies envisioned wider horizons for a national organization that has, in fact, been remarkably successful in the initial achievement of these aims.

Herein lies a situation that is a little curious. In contrast to the increasing vigor of the national Society, the component local chapters are, in many instances, much less active than they were in our formative period. Outfits like the huge American Medical Association owe much of their strength to the grass roots county medical societies. Almost all of the national subspecialty groups have local assemblies which parallel their national meetings. Whereas the Nuclear Society Chapters languish while the national Society as a total group grows stronger.

A common experience of our regional chapters has been that at the time of their organization and for some time after the members enthusiastically supported the new venture. Regular meetings were held and programs presented. Then the activity slowed up. Why was this so?

I venture an explanation which to me appears valid. Each chapter, using the available talent within its own membership, continued to hold meetings and to present programs until its list of subjects and speakers became a little threadbare. Then the interest waned *locally,* but not *nationally* where new subjects and able speakers are constantly available.

It is not surprising that this should happen; it has happened to other societies that have remained too closely constricted within themselves. But The Society of Nuclear Medicine should do something about this situation. And do it we can and with much profit to everyone concerned providing the local membership takes a good long look at our objectives and aspirations as national leaders in this new field of scientific effort.

What are these objectives? Most of them are obvious and need not be here enumerated. One of them, however, is pertinent to this discussion and supplies an adequate answer to our dilemma. We are committed, as a Society, to the expansion of radioisotopic techniques in areas not yet employing these highly efficient, accurate and often simplified methods.

Let me illustrate. Had clinical laboratory specialists confined their efforts to their own society membership, the entire profession of medicine would not now be concerned with acid-base and electrolytic balances. Had cardiologists isolated their skills within their own limited societies, the American public would not now be deeply interested in coronary artery disease. These developments occurred because the experts in these fields widened their base of operations.

Let me come to the point at issue with a concrete proposal to our entire membership. Let every chapter put on two meetings a year, spring and fall. Let one of these meetings be given over to the works-in-progress of the local chapter membership. Let the other meetings be open to the entire scientific public, including county and state medical societies, universities, instrument people and industry. Let the publicity be widespread by letter, newspaper, TV, through hospital staffs, etc. Let the programs be beamed toward those in other fields that seek a working understanding of isotopic applications and methods. Often a university or a private hospital will cosponsor such a meeting.

Will this system work? The answer is an emphatic yes. I speak from experience. We have staged annual one-day meetings on four or five occasions and have never failed to draw an audience of several hundred persons. At the time we started this system, a single paper on this subject was not acceptable to the Colorado State Medical Society. Recently that same society devoted a three-day meeting to the radioisotopes.

If help is needed to assemble national experts in the field, The Society of Nuclear Medicine will cooperate. But let's get this program rolling to the good of the Society and to the advancement and influence of its local chapters. The new field of radioisotopes in science and industry is destined to expand; no one argues against this obvious fact. And The Society of Nuclear Medicine will gain leadership in proportion to how well we function as a *total* Society at both local and national levels.

How about it; will your chapter again take over? Let us know what you are doing so that it can be written up in the Journal.

CALENDAR OF EVENTS

Date		
September, 1963		
6-7	Meeting of the Nuclear and Radiation Chemistry Technical Group of the German Chemical Society	Karlsruhe-Leopoldshafen, Germany
19-20	International Conference on the Industrial Applications of Radioisotopes	Zurich, Switzerland
October, 1963		
1-4	Annual Meeting of the American Roentgen Ray Society	Montreal, Canada
7-11	Symposium on Biological Effects of Neutron Irradiations	Vienna, Austria
17-19	Southeastern Chapter—Society of Nuclear Medicine	Bal Harbor, Florida
21-25	Seminar on Medical Radiation (Limited Attendance)	Ottawa, Ontario, Canada
November, 1963		
17-22	Radiological Society of North America	Chicago, Illinois
18-21	Joint Winter Meeting of the American Nuclear Society and the Atomic Industrial Forum and Atom Fair	New York, New York
19-21	Meeting of the American Physical Society	Norman, Oklahoma
December, 1963		
19-20	Symposium on Radiation Emergencies in Medicine, Research, and Industry	Chicago, Illinois
January, 1964		
	6th International Symposium on Radioactive Isotopes in Clinical Medicine and Research	Bad Gastein, Austria
February, 1964		
5-8	American College of Radiology	Tucson, Arizona
March, 1964		
	5th Inter-American Symposium on Peaceful Application of Nuclear Energy	Chile
20-22	Southwestern Chapter—Society of Nuclear Medicine	Houston, Texas
April, 1964		
13-16	Annual Meeting of the American Radium Society	White Sulphur Springs, West Virginia
June, 1964		
17-20	*11th Annual Meeting of the Society of Nuclear Medicine*	*Berkeley, Calif.*
August, 1964	8th Inter-American Congress of Radiology	Caracas, Venezuela
June, 1965		
16-19	*12th Annual Meeting of the Society of Nuclear Medicine*	*Bal Harbour, Florida*

This Calendar of Events will contain basic information on special courses and meetings of interest to members of The Society of Nuclear Medicine. If you desire more complete information, Mr. Samuel N. Turiel, Administrator of The Society will be pleased to supply you with the name and address of the convening body or sponsoring organization, upon receipt of your request.

JOURNAL OF NUCLEAR MEDICINE 4:417-425, 1963

Radioisotope Placentography: A Bedside Procedure[1,2,3]

Millard N. Croll, M.D.,[4] Larry H. Shuman, M.D.,[5] Leonard Stanton, M.S. and Casimir Czarnecki, M.D.[6]

Philadelphia

INTRODUCTION

The patient who develops bleeding in the third trimester of pregnancy presents what often is a very difficult diagnostic problem. Placenta praevia and premature separation of the placenta are the primary situations to be differentiated. The treatment of the two conditions may be different. Therefore, it is important to determine as precisely as possible the location of the placenta and, in particular, to know if it is implanted near the cervical os. Vaginal examination may be limited by inadequate cervical dilatation and may be quite hazardous by precipitating massive hemorrhage. Diagnosis has been mainly by radiographic soft tissue examinations, contrast studies, or displacement techniques. The clinically useful roentgenographic procedures have a variable reliability up to about 85 per cent (15) but all too often are dependent upon the quality of the roentgenograms. Kimbrough (8) has pointed out that the soft tissue x-ray technique is valuable, but dependable only in ruling out placenta praevia, therefore it is a diagnosis by presumption.

Browne and Veall in 1950 first reported the application of radioactive sodium-24 techniques for localization of the human placenta (2). This was developed initially as a more reliable method of observing circulatory physiology of the placenta. In 1956, Weinberg, (17) elaborated this research technique into a practical means of placentography. The major shortcoming was found to be an extremely rapid diffusion of the Sodium-24 from the circulation necessitating rapid counting and relatively high levels of radioactivity.

Weinberg *et al* (16) reported in 1957 that I^{131} labeled human serum albumin was retained in the maternal circulation for a long period of time. Since then, further experiences have been reported by various authors (3,4,5,7,9,13).

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[1]Presented at the Ninth Annual Meeting of Society of Nuclear Medicine, Dallas, Texas, June 29, 1962.

[2]From the Departments of Radiology and Obstetrics and Gynecology, Hahnemann Medical College Philadelphia, Pa.

[3]This study was supported by the Squibb Institute For Medical Research and the American Medical Research Foundation Grant Number 9.

[4]Advanced Clinical Fellow in Radiation Therapy, American Cancer Society.

[5]Present address: Department of Obstetrics and Gynecology School of Medicine, Yale University, New Haven, Conn.

[6]Present address: Nazareth Hospital, Philadelphia, Pa.

The localization of the placenta by a radioisotopic method depends on the concept that the placenta represents a large blood pool wherein the isotope may accumulate and be detected. Radioactive iodinated human serum albumin will remain within the maternal circulation for a period of time sufficient to carry out the study. Based on this experience we have attempted to develop a method of isotope placentography which would be reliable, safe, and convenient.

METHOD

The patient to be examined is given twenty drops of Lugol's solution orally at least two hours prior to the study. Five microcuries of radioiodinated human serum albumin is injected intravenously and ten minutes is allowed for distribution of the material in the maternal circulation. The fetal position and the height of the fundus above the symphysis pubis is recorded and the abdomen is divided into thirteen counting areas by skin marking. (Fig. 1). Direct surface counting is started with a miniaturized scintillation detector[1] fed into a small portable

[1]Baird-Atomic Model MWC-149.

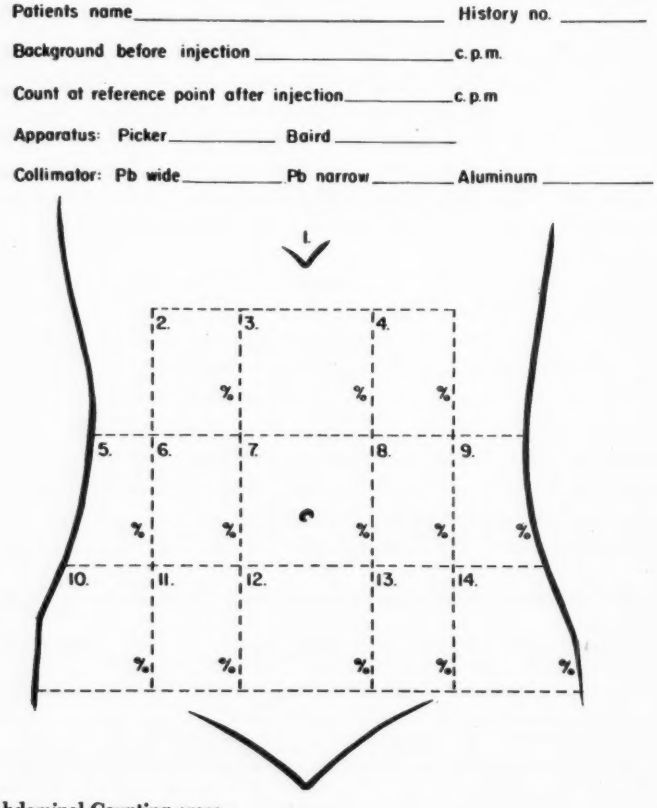

Fig. 1. Abdominal Counting areas.

decade scaler.[2] A count is first taken over the xiphoid process which acts as a reference value. Nine of the counting positions are over the anterior uterine wall and four of the areas are along the lateral walls. In the anterior position, the collimator of the scintillation detector is aligned so that its axis is perpendicular to the skin and uterine surface at the point of the reading. The lateral readings, however, taken in each flank, are made with the detector in a somewhat oblique position so that it can record activity in the posterior aspect of the uterus. In the initial study, all areas were counted in sequence and then repeated.

The patients selected for the study were 1) all patients with third trimester bleeding; 2) all elective Caesarean sections in whom verification of the placental site could be made; 3) patients with a suspected intrauterine fetal death; 4) patients with polyhydramneous in whom transabdominal amniocentesis might be indicated, for prior localization of the placenta; 5) all patients with either malpresentations, unstable lie or high fetal head, since these abnormalities often are related to an abnormal placental implantation.

[2]Baird-Atomic Model 123.

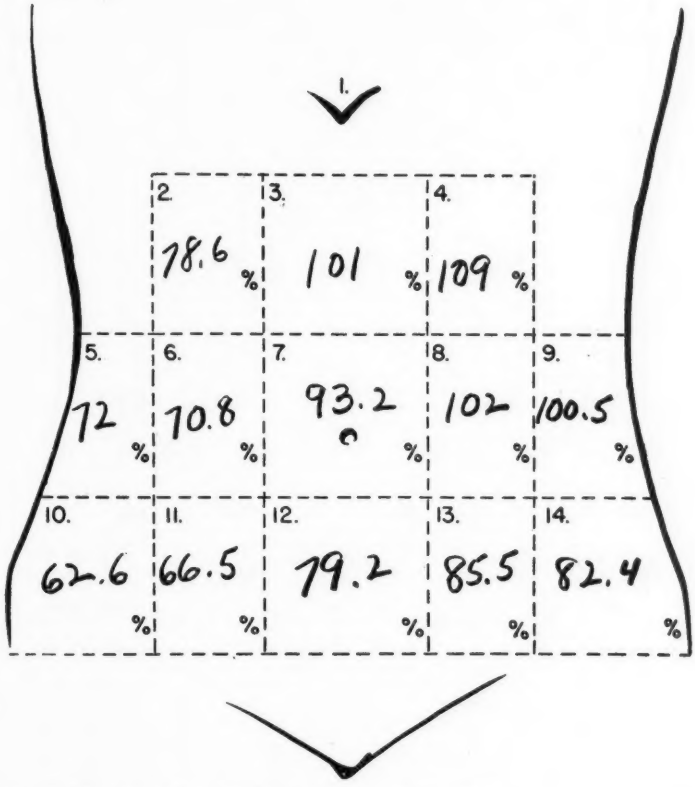

Fig. 2. Placenta localized in the fundus, anterior and on the left.

TABLE I

RESULTS

Total patients studied	57
Suspected clinically of placenta praevia	13
Correctly identified	12
False positive	1
False negative	0
Incorrect localization	5
Correct localization	51
Diagnostic accuracy	89.5%

INTERPRETATION

The normally implanted placenta lying high in the fundus will show an increase in radioactivity in the superior portion of the uterus with a decreasing rate as one goes caudad. Placenta praevia, on the other hand, will show the major portion of activity over the symphysis pubis or if it is a marginal placenta

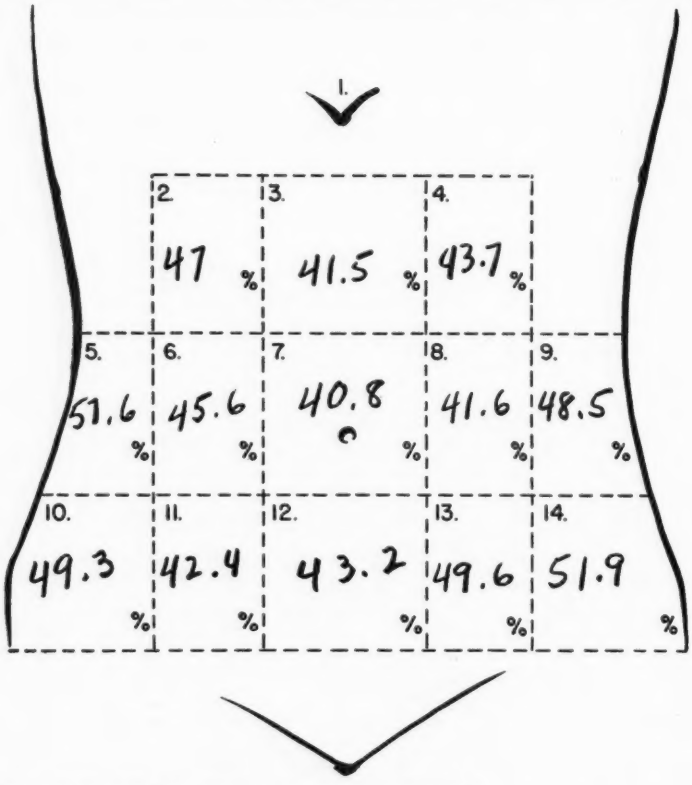

Fig. 3. Placenta located diffusely on the posterior uterine wall.

praevia, the activity will be highest at the lower lateral walls. The anterior placental location can be determined with relative ease and accuracy. The posterior placenta yields a decreased counting rate over the anterior abdomen but the lateral counting areas show a significantly increased rate. Figures 2, 3, 4, 5, and 6, demonstrate various areas of localization.

RESULTS

The findings are summarized in Table I. Fifty-seven patients have been studied. Thirteen were suspected clinically of placenta praevia. Twelve were correctly localized and one patient was diagnosed as marginal placenta praevia but at operation had a succenturiate lobe near the internal cervical os. One patient with suspected intrauterine fetal death was correctly identified by the decreased vascularity. Five patients were incorrectly localized yielding an overall diagnostic accuracy of 89.5 per cent. Confirmation of results was by Caesarian section or manual extraction of the placenta at delivery.

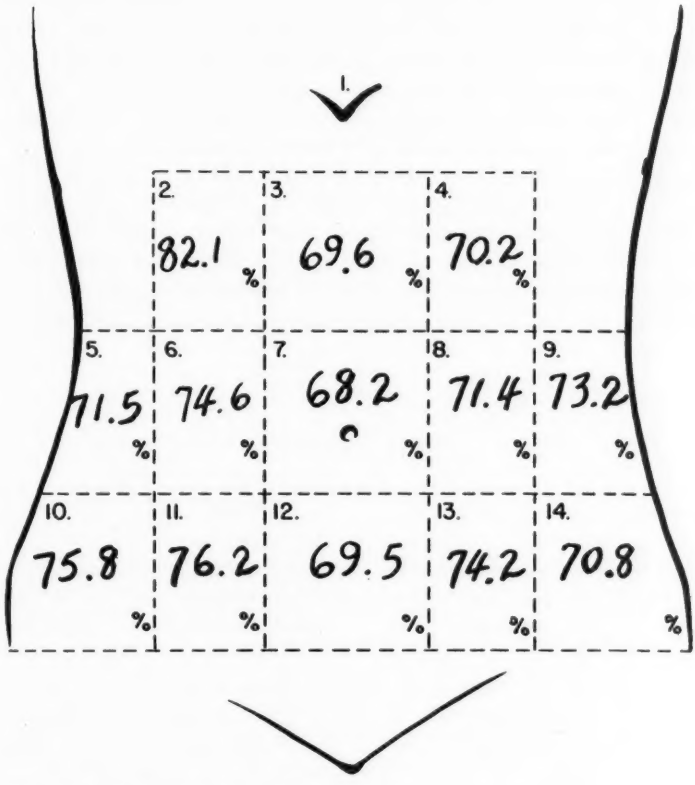

Fig. 4. Placenta located on the anterior uterine wall.

DISCUSSION

Considerable attention has been paid to the radiation hazard of the procedure. The major considerations are the whole body, the gonadal and the thyroidal radiation dosages received by both the mother and the fetus. The radiation dosage measurements are based upon the study in each patient of the post-partum placenta, a sample of cord blood, the maternal thyroid, the maternal peripheral blood and urine, the fetal thyroid, and the fetal peripheral blood. Our results compare favorably with the original findings of Hibbard and Hebert (6) revealing that the procedure as described results in an average total body radiation exposure to the mother of 15 millirads and to the fetus of 6.5 millirads. In calculating the total body radiation dosage we have followed the procedure of Heagy and Swartz (5) assuming the radioactive iodinated human serum albumin is distributed uniformly throughout the maternal circulation and that the total radioactive decay is within the body. We have, therefore, neglected the biological excretion and have made the effective half-life equivalent to the physical half-life of the isotope. The calculations then were made from the standard formulas by Quimby, *et al* (11).

The activity in the cord blood was found to be less than 1 per cent of the specific activity of the maternal blood and it would appear that little of the radioactivity circulates in the fetus. Actually, the main source of fetal total body radiation dosage results from the gamma activity of the I^{131} in the maternal circulation. These findings confirm the predicted impression that radioiodinated human serum albumin is confined to the maternal circulation.

The radiation dosage to the fetal thyroid has been an area of controversy. The original work of Hibbard and Hebert was performed with no attempt to block with stable iodine the maternal or fetal thyroid gland. They computed radiation to the fetal thyroid of approximately 1 rad per microcurie of I^{131} albumin administered. Because the iodinated human serum albumin is confined predominately to the maternal circulation the majority of the fetal thyroidal

TABLE II

DOSAGE CALCULATIONS

Individual	*Area*	*I^{131} RISA*	*Roentgenograms 2 Exposures*
Fetus	Whole body	6.5 mrads	1000 mrads
	Gonads	5.0 mrads	1000 mrads
	Thyroid	*2500.0 mrads	1000 mrads
Mother	Whole body	15.0 mrads	——
	Gonads	12.0 mrads	1000 mrads
	Thyroid	* 250.0 mrads	5 mrads

*Dose without thyroid blocking by Lugol's Solution.

radiation dosage results from the gamma component of Iodine-131 circulating in the mother rather than from concentration of inorganic I^{131} in the fetal thyroid.

The inorganic I^{131} available results from small amounts of contaminant in the radioactive albumin and from the metabolic degradation of the injected albumin with the liberation of I^{131} into the maternal circulation. Inorganic iodine from the albumin molecule is liberated in the body at a rate of 5 per cent per day (1).[1] This means that with an injected dose of five microcuries, 0.25 microcuries inorganic I^{131} is available each day for thyroidal uptake (12). Calculations based on this rate of degradation and this injected dose indicate that the maximum total radiation dosage to the fetal thyroid is 2500 millirads in the average patient. The administration of Lugol's solution prior to the radioactive material can effectively block the uptake of I^{131} by the thyroid and minimizes specific irradiation of the gland. These radiation dose levels may be compared with the average roentgenographic exposure for two

[1]The rate of degradation varies greatly with the pharmaceutical purity with rates up to 30 per cent per day being reported (10).

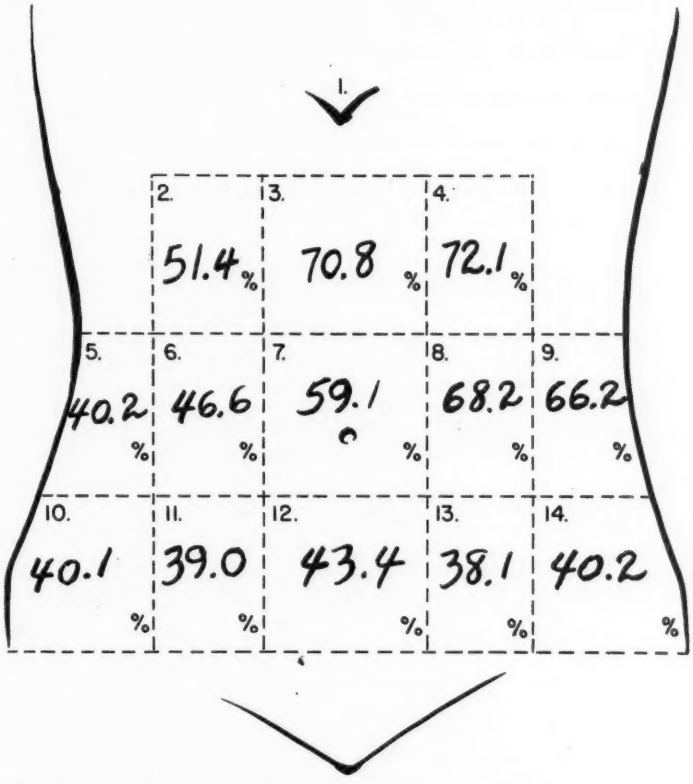

Fig. 5. Placenta lying on the posterior-superior uterine wall on the left.

abdominal scout films of 1,000 millirads to both the abdomen of the mother and the total body of the fetus (14). These calculations are summarized in Table II.

Efforts are now being directed toward making this a truly bedside procedure. The placental localization can be performed in the labor room with a small and lightweight scintillation probe and scaler. To enable successful use as an emergency procedure at night by the radiological or obstetrical resident on call, a pre-calibrated disposable syringe of I^{131} serum albumin is available.

SUMMARY

1. Localization of the human placenta by a radioisotopic method utilizing Iodine-131 human serum albumin is reliable, safe and convenient.

2. The accuracy of localization of the placenta has been excellent. Determination of clinically suspected placenta praevia was correct in 92.3 per cent (12 of 13 patients).

3. Radiation dosage to the maternal abdomen and gonads and fetal whole

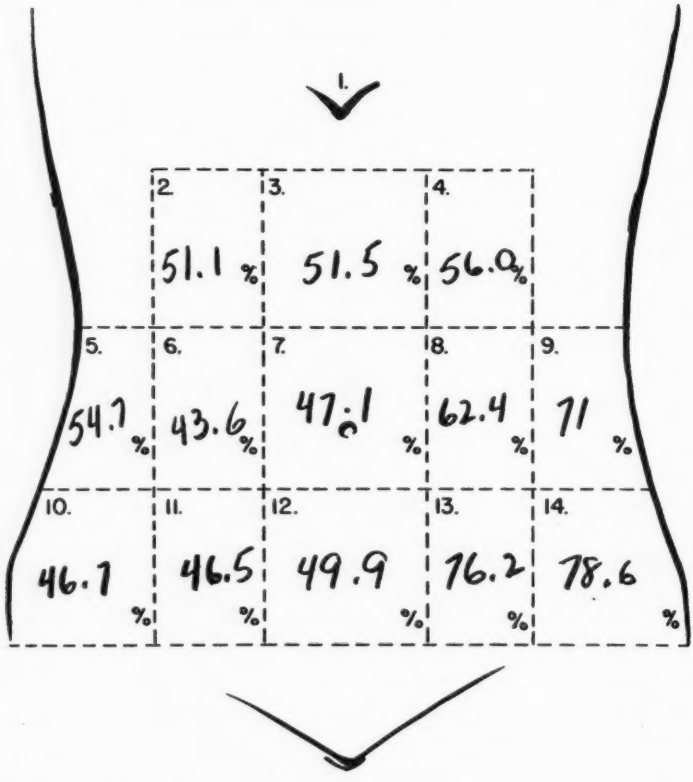

Fig. 6. Left placenta praevia marginalis.

body radiation dosage have been reduced far below what is received by the usual roentgenographic study.

4. The procedure is a truly bedside examination with lightweight portable equipment and precalibrated doses of the radioisotope.

ACKNOWLEDGEMENT

The authors wish to gratefully acknowledge the technical assistance of Gloria S. Sword, R. T.

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Liquid Scintillation Counting of I^{131} in a Clinical Laboratory[1]

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INTRODUCTION

The liquid scintillation counter, generally regarded as a research tool, is of great potential value in a clinical isotope laboratory. The instrument has a unique ability to count, with high efficiency and low background, and with 4π geometry, beta emissions from comparatively large samples. Positron emitters and nuclides emitting certain other particles can be similarly measured, and beta-gamma emitters can sometimes be counted with greater sensitivities than are commonly achieved in conventional clinical gamma counting equipment. Utilization of the liquid scintillation counter for clinical work, however, has in essence, been hampered by difficulties in the preparation of samples. A voluminous literature exists describing many different techniques for sample preparation, some of which involve several chemical manipulations. By contrast, gamma counting entails little or no pre-treatment of the specimen.

The basic difficulty in preparing biological materials for liquid scintillation counting has been in trying to dissolve aqueous organic materials in scintillator fluids such as toluene. Additional problems of chemical quenching, color quenching, and phosphorescence are also encountered, but correction factors can be applied to compensate for these phenomena. If, therefore, *a simple method of sample preparation* is made available, the development of new techniques for clinical tests and research will be facilitated. A variety of beta emitters such as C^{14}, S^{35}, P^{32}, etc. and certain other radionuclides could be used for routine work on human subjects at very low tracer dose levels.

Many approaches have been made to the problems of determining beta radioactivity in aqueous solutions (13) and heterogeneous systems (14) by liquid scintillation techniques. Standard procedures for organic materials include Van Slyke-Foch wet oxidation, dry combustion at high temperatures (Schoniger)

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and many other methods and modifications(26). C^{14} and Tritium are by these methods converted to carbon dioxide and water. Isotopes of calcium, sulfur, iron, and others can also be similarly extracted from organic materials. Recently, solubilizing agents such as Hydroxide of Hyamine, or Alcoholic KOH have been used to dissolve small amounts of blood or tissues(17) to form solutions miscible with various scintillator solutions. The latter can, if necessary, be tailor-made for specific purposes (19). With biological materials, color quenching reduces efficiency(17), the size of the sample may be limited, and furthermore, the sample preparation technique may be tedious and time consuming.

Another approach is the suspension of finely divided but insoluble solids in a gel scintillator(15) such as "Cab-O-Sil." or "Thixin". It is claimed that quantities of 1 gram or more of some compounds can be counted at high efficiencies in this way (16). The material needs to be in the form of a dry powder for counting. Although chemical quenching does not occur in such a system, since there are no quenching substances in solution, counting efficiency may be reduced by light scattering due to opacity of the system and by self-absorption by the sample of the lower energy beta emissions. These effects become more pronounced as the amount of dispersed solid per unit volume of scintillator increases. An emulsion of Hyamine and Toluene scintillator with Thixin gel as a suspending agent has also been used to count aqueous samples of C^{14} and Tritium, but these emulsions tend to be unstable(18).

Davidson(19) reviewed recent developments in techniques for liquid scintillation counting. There has been increasing interest in recent years in the use of

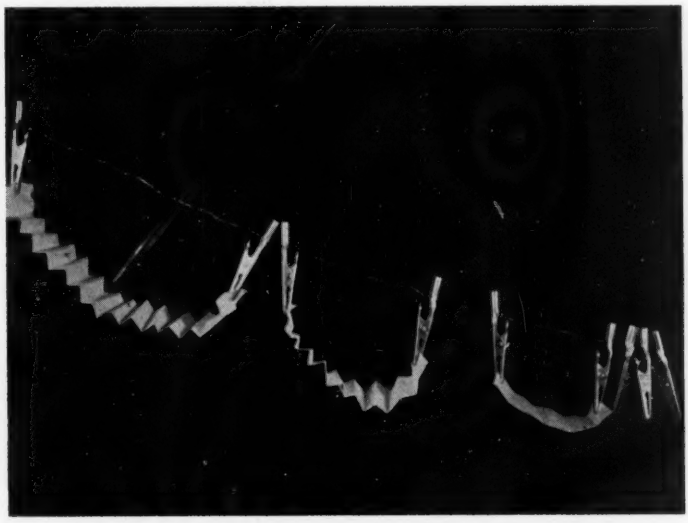

Fig. 1. The paper strips have been folded in concertina fashion in order to facilitate uniform distribution of the sample and to minimize pooling. The sample is distributed along the length of the paper from the pipette as shown.

paper for suspending insoluble materials in scintillator fluids. The method is attractive since purification and special preparation of the sample are not required. The technique springs from the now well-tried method for determining beta activity on paper chromatograms or electrophoresis strips (1) (21) (22). It has been found that in order to measure beta radioactivity in various parts of a chromatogram, the paper can be divided into strips or sections of suitable size and the strips counted directly in vials of scintillator fluid. Certain problems associated with this technique and relevant to the work described below will be discussed later. The method, which gives much greater efficiencies than obtainable with moving strip gas flow techniques(20), is applicable for substances insoluble in the fluid. Insolubility is, in fact, an asset if the substance is supported on paper (12). Elution of the material from the paper, which is sometimes tedious and may not be quantitative, is unnecessary for most counting purposes, although there may be certain specific reasons for doing this (7).

In the Radioisotope Laboratory at the Cincinnati General Hospital, liquid scintillation counting has been used in the analysis of chromatograms made from blood and urine of thyroid patients after administration of I^{131}, and this work is to be reported elsewhere. As the counting efficiency for I^{131} beta particles under these circumstances was noted to be very high (approximately 75%), and background very low (approximately 30 counts per minute), possibilities for developing a paper method for other clinical applications immediately suggested

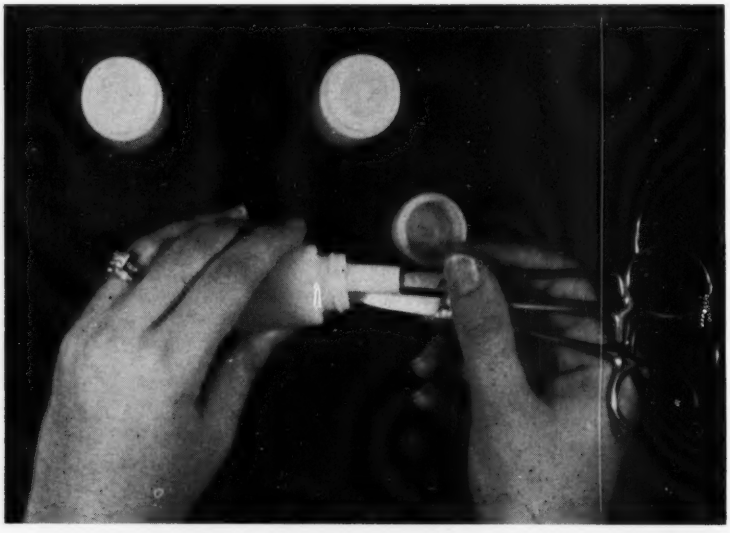

Fig. 2. The paper, after thorough drying, is tightly rolled into a cylindrical form and placed in the standard polyethylene counting vial. Subsequently, scintillator fluid is added in quantity sufficient to completely cover the paper, and the specimen is ready for counting.

themselves. Specifically it was decided to evaluate the paper technique as a potentially useful method for counting I^{131} in *unprocessed* plasma. Since it was theoretically possible to extend the paper size, the sample fluid volume could also theoretically be increased to approximately the same as that used in conventional gamma well-counting. The sample would therefore be *deliberately* placed on paper which would act as a matrix to hold the radioactive material suspended as a thin film within the scintillator fluid. Intimate contact between insoluble isotopic material and scintillator fluid would thus be facilitated. A similarity to the gel system for suspending insoluble materials is obvious; however, the paper method simplifies sample preparation. If filter paper is transparent to the scintillation photons(19), the presence of paper has no effect on the system and interaction between beta particles and phosphor can take place within the fibers of the paper. Color quenching and opacity due to the sample can be corrected for, if encountered.

REVIEW OF THE LITERATURE

THE PAPER. Many of the reports published on the paper suspension of sample concern the estimation of radioactivity (usually of a C^{14} or Tritium compound) on paper chromatograms. Some workers, however, deliberately dried samples onto small paper discs(2) (3) (4) generally 2-3 cm in diameter, or onto paper squares(5) (6) (7) (8) (9) of approximately the same size. The orientation of the paper within the vial relative to the photomultipler tubes is of importance for low energy beta emitters such as C^{14} and Tritium, (8) (9) (10) (11) (12) and, in the interest of constant geometry, small paper discs resting at the bottom of the counting vial have been used (3) (5) (7). Loftfield (11) (12) found that if the paper is rolled into a cylindrical form, and is placed vertically in a test tube filled with scintillator within a standard 5 dram counting vial, precise and reproducible data are obtained at the expense of some slight loss of efficiency. The total amount of paper used in all the reports studied is generally small, although it is stated that the quantity of paper does not affect counting efficiency (2) (9) (10).

The type of paper used has varied among different writers. Whatman #1 seems to be generally favored, (2) (4) (5) (9) (10) (20) but Whatman #30 (6), Whatman #3MM (3) and other types have also been used (7) (12). Loftfield (12) found differences in counting efficiency due to paper thickness (2 different types tested). Blair and Segal (9) report that Whatman #5, Whatman #42, and Whatman #1 gave identical counting rates for C^{14} gluconate. It seems that in general Whatman #1 paper (which is approximately 150 microns thick) is most suitable and that thicker papers may be less satisfactory since they may allow a thicker sample to be formed and hence introduce errors due to self-absorption. Our own experience with the thicker (Whatman #3MM) paper has led us to discard it in favor of Whatman #1. At the present time, therefore, further research into the question of paper type is not merited, since Whatman #1 is suitable for the technique and gives constant reproducible results.

It has been emphasized (5) (11) (12) that drying of the paper should be complete, particularly if a non-water miscible scintillator fluid such as Toluene-PPO-POPOP is used. Oven drying or drying in vacuo has been advocated since small quantities of water left on the paper may cause quenching, unless a scintillator solution (such as "Diotol")[1] which will absorb some water, is used.

THE SAMPLE. If the sample is partially soluble in the scintillator fluid, then inconsistent results may be obtained due to variable diffusion of the activity into the fluid(1). Insolubility is, in fact, a prime requirement for the technique, and can be easily tested for by counting the vial of scintillator fluid after the paper has been removed. If counts above background are obtained, then partial solubility of the sample must be suspected. On the other hand, attempts have been made to extract the whole sample from the paper using Hyamine or other

[1]"Diotol" is a commonly used scintillating solution and is made up as follows:—Toluene, 250 ml; Dioxane, 250 ml; Methanol, 150 ml; Naphthalene, 52 gr; PPO, 3.25 gr. and POPOP, 6.5 mgm.

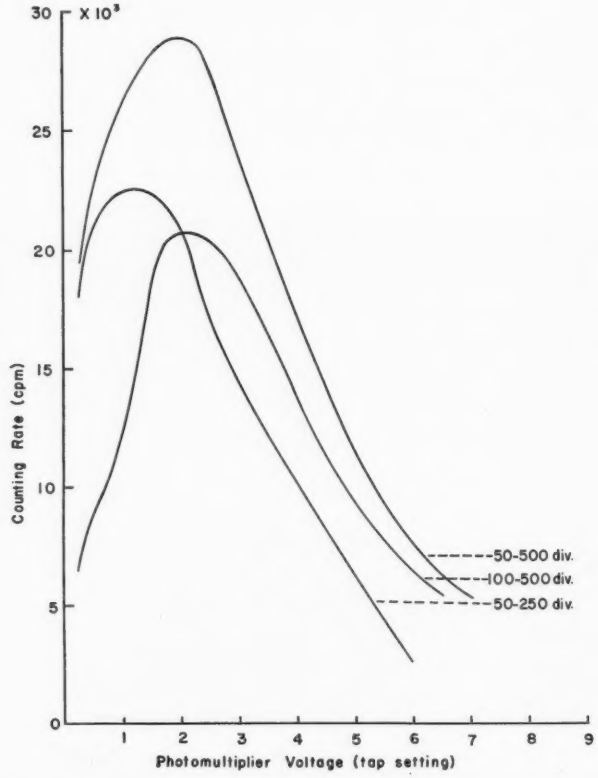

Fig. 3. Typical family of curves for Iodine^{131} beta particles (settings used in the experiments were high voltage tap 1, wide window 50-500 divsions).

suitable solvent before counting, and it has been found that in order to obtain reproducible counts and estimates of absolute radioactivity, extraction of the sample from the paper must be over 80 per cent(7). It follows from these two considerations, that the sample must be either completely insoluble, or completely soluble in the scintillator, for the paper counting technique. Partial solubility, perhaps due to mixed labelled compounds may give misleading results.

QUENCHING AND SPECIFIC ACTIVITY. In general, quenching is dependent on the nature of the sample and may be a difficult factor to evaluate in heterogeneous systems, such as plasma. Theoretically, with a pure, dry, insoluble sample, chemical quenching cannot occur; however, KOH treated papers can cause some quenching (5) (6). If quenching substances are present in the sample, their action can be minimized by using maximum amounts of scintillator fluid, so as to dilute these agents (7). Methods for investigating and correcting for quenching have been well described (6) (7).

It has been stated that protein material or amino acids in the sample in "substantial amounts" (actual amounts unspecified) do not cause quenching when counting C^{14} or Tritium (3) (12). It might be expected that as the deposition of the sample on the paper becomes thicker, self-absorption may be introduced, at least for weak beta emitters (9). This factor can be minimized by selecting the appropriate voltage setting on the machine. It is likely that sample weight will be unimportant if the sample is spread thinly over a large enough piece of paper, and that for high energy beta emitters such as P^{32} and I^{131}, the effect is probably negligible. Changes in efficiency due to sample weight (for a standard size piece of paper) must be born in mind, however, if measurements of absolute radioactivity are to be made. For any standardized counting system, a linearity must be demonstrated between applied activity and count rate independent of specific activity.

THE SPECTRUM. Loftfield, et al (11) (12) showed that two chemically related C^{14} labelled substances (valine C^{14} and valine C^{14} hydroxamate) have different liquid scintillation spectra. In practice, this difference means that for given machine settings and a given window, the efficiencies for C^{14} might depend on the chemical form of the labelled compound. A "quenching" phenome-

TABLE I

LIQUID SCINTILLATION COUNTING OF I^{131} BETA PARTICLES, PARAMETERS STUDIED

1. Optimum concentrations of primary and secondary solutes.
2. Scintillator fluid volumes.
3. Filter paper sizes (length, thickness).
4. Limitations of plasma volumes.
5. Effect of plasma sample location on paper.
6. Possible color quenching effects of plasma.

non, causing a spectrum shift, is probably responsible for this effect. Such observed differences in apparent efficiencies may be a source of error for the unwary. If the extent of the spectrum shift is known, the data can be corrected for differences in efficiency; or alternatively, a tap setting on the machine can be selected for which the efficiencies for the two substances are identical. It is not known whether this phenomenon has been observed for other isotopes or other compounds, and if effects of this type might be seen in a heterogeneous system such as plasma. It is suggested, therefore, that spectral differences be tested for, before placing reliance on experimental data concerning two or more substances similarly labelled. Machine settings can then be selected so that the different substances can be counted at the same efficiency.

PRESENT INVESTIGATION

Although many different beta emitters, beta-gamma emitters, positron emitters, and nuclides emitting internal conversion electrons can be counted in a liquid scintillation system, we have been preoccupied with I^{131} since it is an isotope of considerable clinical interest. Our studies, therefore, concern the measurements of I^{131} *in plasma,* although the methods to be described could be adapted for many other radionuclides. In attempts to optimize a technique such as this, it is necessary to study systematically, in relation to efficiency and background, factors such as the limitations of the paper size, limitations of sample fluid volume, effect of color, suitability of different types of scintillator solution, etc. Some of these factors have been evaluated and the results are now presented.

TECHNIQUE

For the experiments, a known amount of I^{131} (carrier free) was added to plasma. This plasma was then pipetted onto strips of Whatman #1 filter paper, 1¾″ wide. (Fig. 1) It was found that this paper would absorb 1 ml plasma for each 6″ of its length. Thus, 3 ml of plasma may be used on 18″ of paper. After complete drying, the paper is rolled up and inserted into a polyethylene vial (Fig. 2). Scintillator fluid is added and the vial is counted in a Packard "Tri-Carb" liquid scintillation spectrometer at the appropriate settings providing maximum merit value for the I^{131} beta particles (high-voltage tap 1, gain 1000, wide window 5-50 volts). A typical family of curves of counting rate against photomultiplier voltage for various discriminator settings is shown in Figure 3. A cesium-137 sample (prepared in the same manner by drying cesium chloride solution on paper) served as a long-lived mock-Iodine beta-standard for checking daily operation of the spectrometer. Cesium has predominately a .51 Mev beta energy as compared to the .608 Mev (87.2%) beta energy which is the prominent one for I^{131}. Because the I^{131} beta energy is relatively high compared to the beta energies of radionuclides normally counted by the liquid scintillation method (C^{14}, S^{35}, H^3), a systematic investigation was undertaken to define the problem specifically for the I^{131} beta particles and for low levels of activity in plasma volumes up to 3 ml. A sample counting time of 30 minutes was selected.

A preliminary experiment showed that the maximum merit value was obtained using standard concentrations of primary and secondary solutes (5 gm/liter PPO and 100 mgm/liter POPOP). It was also determined that the solubility of dried plasma in the scintillator fluid was minimal. Upon removal of the filter paper carrying dried radioiodinated plasma from the counting vial, only 0.2 percent of the radioactivity was found in the fluid (even after the paper had been immersed in the fluid for three days).

The parameters studied in a series of experiments are shown in Table I. With the help of a factorial experimental design (24) it was possible to study several parameters in a single experiment (Fig. 4). Data was obtained for four plasma volumes, four scintillator fluid volumes, and six paper lengths with one observation per cell in the block design. The data was subjected to analysis of variance techniques to determine the effect of the parameters on background, efficiency, and merit value, (Table II).

TABLE II

EFFECT OF VARIOUS PARAMETERS ON BACKGROUND, EFFICIENCY AND MERIT VALUE

Parameters	*Degrees of Freedom*	*F Values*[1]		
		Background	*Efficiency*	*Merit Value*
S	3	0.3	26.5**(−)	20.0**(−)
P	5	1.2	2.9* (−)	2.4* (−)
F	3	31.4**(+)	18.2**(+)	4.0* (+)
SP	15	2.0	2.0	1.3
SF	9	.7	1.2	1.0
PF	15	1.1	1.1	1.0

S—plasma volume (0.1, 0.3, 0.5, 1.0 ml.)
P—paper length (6, 8, 10, 12, 15, 18 inches long)
F—scintillator fluid volume (3, 6, 10, 15 ml.)
*—significant at .05 level **—significant at .01 level
(+) (−)—effect increased (+) and decreased (−) with increasing parameter.
[1]—determined from techniques of analysis of variance.

Background was not affected by increasing plasma volume or increasing paper length, however background increased with increasing scintillator fluid volume. The efficiency and merit value (which is obtained by efficiency squared divided by background) decreased by a small but statistically significant amount with increasing plasma volume and increasing paper length, and increased with increasing scintillator fluid volume. The analysis indicated no significant interactions between the three parameters as far as background, efficiency and merit value are concerned.

FIGURE 4

	S_1				S_2				S_3				S_4			
	F_1	F_2	F_3	F_4	F_1	F_2	F_3	F_4	F_1	F_2	F_3	F_4	F_1	F_2	F_3	F_4
P_1					S_2F_1 P_1											
P_2		S_1F_2 P_2														
P_3											S_3F_3 P_3					
P_4							S_2F_3 P_4									
P_5				S_1F_4 P_5												
P_6														S_4F_2 P_6		

S_1—S_4 = plasma volume = 0.1, 0.3, 0.5, 1.0 ml.
F_1—F_4 = scintillator fluid volume = 3, 6, 10, 15 ml.
P_1—P_6 = paper length (1¾″ wide) = 6, 8, 10, 12, 15, 18 inches

Fig. 4. The experimental design is illustrated by the grid. Each space represents one specimen, however several observations are made of each specimen by means of the automatic sample changer. The designations in occasional spaces represent sample combinations of factors.

Additional parameters of plasma location on paper and paper thickness were then studied, in addition to extending the range of the previously studied parameters (Table III).

TABLE III

EFFECT OF PARAMETERS AND INTERACTIONS BETWEEN PARAMETERS ON MERIT VALUE

Parameters	*Degrees of Freedom*	*F Values*[1] *(merit value)*
F—Scintillator fluid (15, 20 ml.)	1	.1
S—plasma volume (1, 2, 3 ml.)	2	26.5**(−)
P—paper length (6, 12, 18 inches)	2	12.8**(−)
L—plasma location (inside, center, outside)[2]	2	.6
T—paper thickness (Whatman #1, #3MM)	1	30.0**(−)
FS	2	8.9**(−)
FP	2	1.3
FL	2	.3
FT	2	.4
SL	4	.9
ST	2	.8
PL	4	.7
PT	2	6.0**(−)
LT	2	.7

**—significant at .01 level
(−)—effect decreased with increasing parameter (for T—increasing paper thickness)
[1]—determined from techniques of analysis of variance
[2]—refer to text for explanation

TABLE IV

SENSITIVITY OF LIQUID SCINTILLATION METHOD FOR PLASMA (50 μμc I-131)

Plasma Volume ml.	*Paper Length 1¾" x__*	*Background cpm.*	*Sample cpm.*	*Efficiency %*	*cpm. (net) (95% confidence limits)*
1	6	27	85	52.3 ± 3.7	58 ± 3.7
2	12	27	82	49.8 ± 2.0	55 ± 3.6
3	18	27	79	47.5 ± 1.2	52 ± 3.5

Possible effects due to sample geometry were checked by pipetting the plasma at essentially three areas on the paper: an area which was on the *inside* after rolling up of the paper, *center* area of paper, and area which was on the *outside* after rolling up of the paper. Increasing the scintillator fluid volume from 15 ml to 20 ml did not affect the merit value, whereas increasing plasma volume from 1-3 ml resulted in a small (but significantly different) decrease in merit value. Lengthening the paper again resulted in a small decrease in merit value. Plasma location on paper had no effect on merit value. Increasing the paper thickness (by using Whatman #3MM) resulted in a decrease in merit value.

For larger plasma volumes, a slight coloration was noted. An attempt was made to see if the merit value could be increased by trying to bleach the color by spraying the dried plasma on paper with hydrogen peroxide. The results indicated that although the efficiency increased by a few per cent, background also increased slightly, giving if anything, a slightly decreased merit value. It was, therefore, decided that there was no advantage to using hydrogen peroxide as a bleaching agent for the conditions of this study.

Table IV gives the order of magnitude of the efficiency and the background that is obtained using this technique. Here the efficiencies for 3 plasma volumes and 3 paper lengths are shown. A slight decrease (significantly different) in efficiency is shown with increasing plasma volume. This experiment was repeated for additional levels of I^{131} activity (5,000 $\mu\mu$c and 10,000 $\mu\mu$c). It was noted that the efficiencies for each condition of plasma volume and paper length remained the same for these levels of I^{131} activity. The average efficiency was 48% for 3 ml of plasma and 18″ paper length for the three I^{131} activity levels. Table IV also indicates the reproducibility of the method (each value is the average of 5 samples.) From the 50 $\mu\mu$c data, net counts per minute were calculated for a 10 $\mu\mu$c I^{131} level where both background and sample were counted for 30 minutes (Table V).

TABLE V

SENSITIVITY OF LIQUID SCINTILLATION METHOD

	Background 27 cpm (counted for 30 min.)
	Efficiency 48% (I-131 beta particles)
	3 ml. plasma sample on 1¾″ x 18″ filter paper
10 $\mu\mu$c (counted 30 min.)	gives 10.5 ± 3.0 net cpm (95% C.L.)
5 $\mu\mu$c (counted 30 min.)	gives 5.3 ± 2.7 net cpm (95% C.L.)

In general this method gives approximately 1 net count per minute per $\mu\mu$c of I^{131}. A calculation of the smallest detectable activity (25) obtainable using this technique for the conditions of Table V gives a value of 3.8 $\mu\mu$c in 3 ml. plasma (approximately 1.3 $\mu\mu$c/ml).

SUMMARY

A standard method has been developed for the liquid scintillation counting of I^{131} beta particles in plasma volumes from 1 ml to 3 ml with a counting efficiency of 52.5 per cent to 48 per cent. No chemical preparation of the sample is required. For the purposes of estimating total serum I^{131}, protein bound I^{131} and RISA, this method is practical and simple. Its sensitivity permits reductions of the tracer dose of I^{131} by 2-5 orders of magnitude. Liquid scintillation counting is also a value in chromatographic analysis and quantitation of iodinated compounds in the peripheral blood and in urine. The smallest detectable activity (25) using this technique is approximately 1.3 $\mu\mu$c per ml of plasma using a 30 minute counting time.

We are at present routinely measuring I^{131} conversion ratios in plasma using a tracer dose of 10 μc to the patient, where previously 50 μc had been used for the conventional gamma counting procedure. Experiments to develop similar techniques and to determine maximum merit values for counting I^{131} in whole blood (as well as other beta-emitting isotopes such as P^{32} and Fe^{59}) are in progress.

ACKNOWLEDGEMENTS

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C. C. LUSHBAUGH APPOINTED CHIEF OF APPLIED RADIOBIOLOGY

Clarence C. Lushbaugh, M.D., pathologist recently with the Los Alamos (N.M.) Scientific Laboratory, of the University of California, will join the staff of the Oak Ridge Institute of Nuclear Studies Medical Division effective October 1, ORINS Executive Director, William G. Pollard, has announced.

Dr. Lushbaugh, who has spent the summer as a visiting scientist at the Medical Division, will assume the post of Chief of Applied Radiobiology.

Dr. Lushbaugh is recognized as an expert on radiation damage and is among the foremost authorities on the pathologic effects of radiation accidents. He has also played a leading role in the development of whole body counting in the measurement of body burdens of radioisotopes in patients.

A member of many scientific organizations including the Society of Nuclear Medicine and honorary scholastic fraternities, Dr. Lushbaugh is also a member of the pathology study section of the U. S. Public Health Service.

In Oak Ridge, Dr. Lushbaugh will extend his research in radiobiology, especially as it applies to human beings. As a member of the Medical Division staff he will take part in studies of the use of radioisotopes in diagnosis and treatment of certain diseases, including some types of cancer.

JOURNAL OF NUCLEAR MEDICINE 4:439-445, 1963

Color-Coded Digital Print-Out for Radioisotope Scanning[1]

Gerald J. Hine, M.D

Boston

INTRODUCTION

It has long been recognized that additional information could be obtained from radioisotope scanning, if the data could be presented in counts per unit time as is customary for all other radioisotope tracer measurements. A numerical print-out is extremely helpful for locating areas of increased concentration (1), but is not practical for outlining an organ or the radioisotope distribution within an organ. The various black and white print-out systems delineate the boundary between areas of high and low concentrations very well but might obscure a gradual change in concentration or miss an area of low concentration due to background cut-off selection.

Quantitative information can be obtained from a scan if the color of the print-out changes with the count-rate. Then the printing pattern shows the radioisotope distribution and the printing color indicates the variation in concentration. Two such systems have been developed at Hammersmith Hospital (2, 3). Though the results have been excellent, a color print-out has not yet been used in this country to our knowledge. One of the reasons might be that the system of Mallard and Peachey is rather complex. We have developed a simple method for color printing which can be incorporated in standard scanners. It is in principle similar to Mallard and Peachey's second system (3) which was brought to the author's attention only after completion of our instrument.

METHOD

For the color printing 8 parallel colored typewriter ribbons are employed. They are mounted on rolls on both sides of a carriage with a slit at the center

[1]Radioisotope Service, Boston Veterans Administration Hospital; Department of Medicine, Boston University School of Medicine; and the Boston University Medical Center, Boston, Mass.

where the printing stylus hits the ribbons. The carriage moves the ribbons back and forth beneath the tapper close to the paper. The movement of the carriage is controlled by a count-rate meter with a time constant of 0.3 sec. The output of the count-rate meter is connected to the servomechanism of a stripchart recorder which moves the carriage so that the tapper strikes a particular ribbon selected by the count-rate.

The whole assembly[1] follows the scanning motions. Simultaneously with each printing all 8 rolls are advanced as in a typewriter, regardless of which ribbon is used for the printing. A continuous ribbon drive would work equally well.

The rolls of ribbons are separated from each other by thin plastic spacers. This produces a small gap between the ribbons in the printing area. If the stylus hits the gap between two ribbons, the colors of the two adjacent ribbons are printed with a 1/32-inch blank space between.

Since each ribbon is 0.5 inches wide, the carriage moves 4 inches from zero to 100 per cent. The travel time for this distance is about 1 second which is sufficiently fast since the scanner must move at least that period of time to reach extremes of high and low areas of radioactivity.

Certain colors of typewriter ribbons which are commercially available were arranged according to the rainbow spectrum with red on one end and purple on the other. Actually, only 7 colored ribbons are used with one uninked. Since they are of equal width, each ribbon covers a 12.5 per cent interval of the 100 per cent maximum. The lowest 10 to 20 per cent practically always represents tissue background and therefore the first ribbon is colorless, setting in effect a fixed cut-off level. However, in contrast to other systems employing a background cut-off, no information is lost in the case of a colorless print, since all counts are printed in black through carbon paper on a second sheet of paper. The purple follows the blank ribbon while the bright red represents the upper 12.5 per cent (see Figs. 1-4).

Where similar colors are adjacent to each other they are sometimes difficult to recognize as different. For example, blue follows purple and a few blue prints in an area of mainly purple points might easily be overlooked while a contrasting color would stand out. On the otherhand, contrasting colors adjacent to each other yield a confusing picture. Due to statistical fluctuations at low count-rates, a variation of $\pm$ 10 per cent is rarely significant and therefore nothing is lost if similar colors are not always recognized as being different.

In setting up a scan two selections must be made. First, the area of highest count-rate is located and the output of the ratemeter is adjusted to the 100 per cent level. In practice the count-rate is fluctuating and it is difficult to know exactly where the highest intensity will be reached. It is sufficient to adjust at the 90 per cent level within an area of apparently high count-rate. The second choice is that of a scale factor for the printing. For a maximum count-rate of about 3000 cpm we print every eighth count, and higher count-rates require

[1]Built by Laboratory Associates, Belmont, Mass.

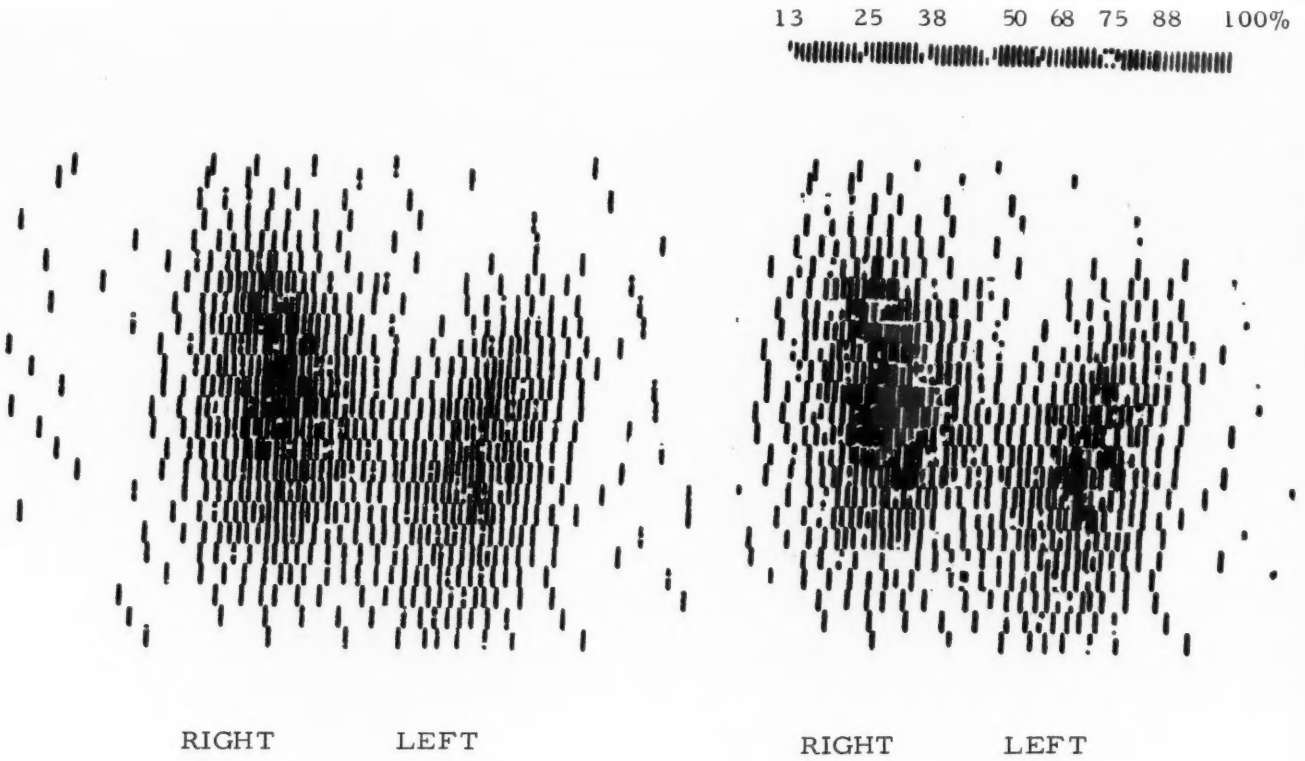

Fig. 1. Thyroid scan with 8.7 μc I^{131} in the gland (carbon copy and color print). By using the Picker 19-hole collimator some resolution is sacrificed for statistical accuracy (scale of 32 for printing). Scanning in one direction from right to left only; shift of colors to the left due to scanning speed of 4 mm per second which is high for a thyroid scan. A difference of about 30% more radioactivity in the right lobe can be estimated from the color print.

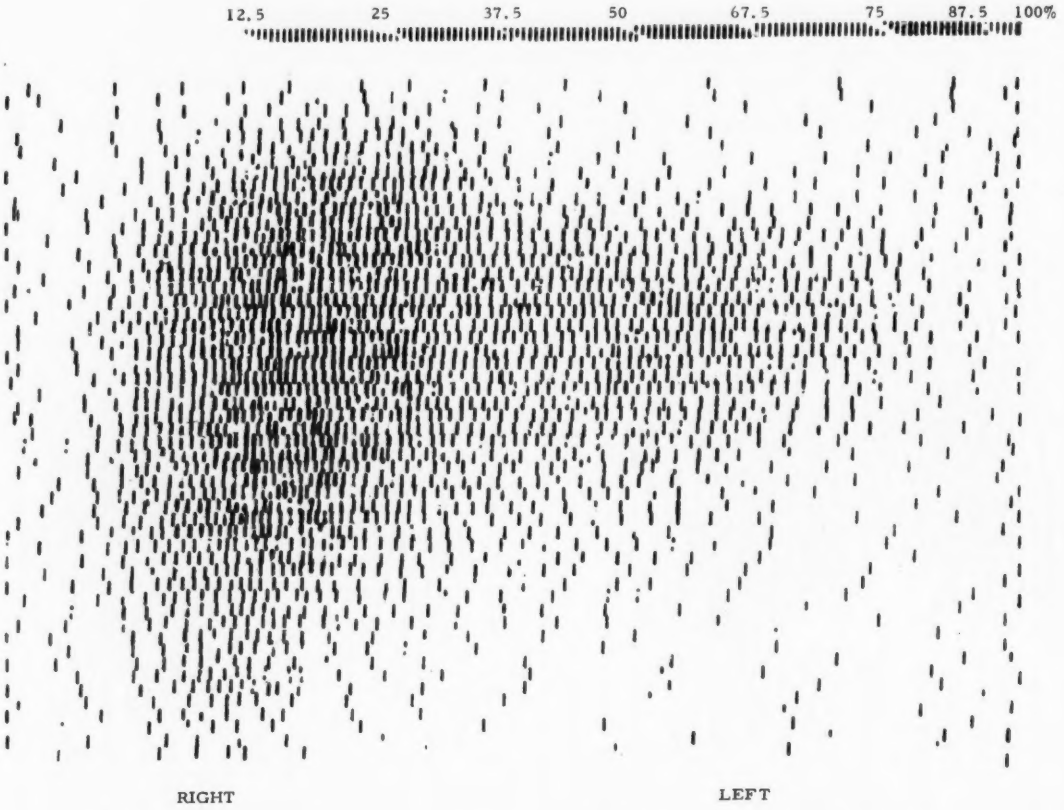

Fig. 2. Liver scan with a dose of 54 μc Au^{198}. Scanning speed 6 mm per second; scale of 32 for printing. The colors reflect variations in the thickness of a normal liver.

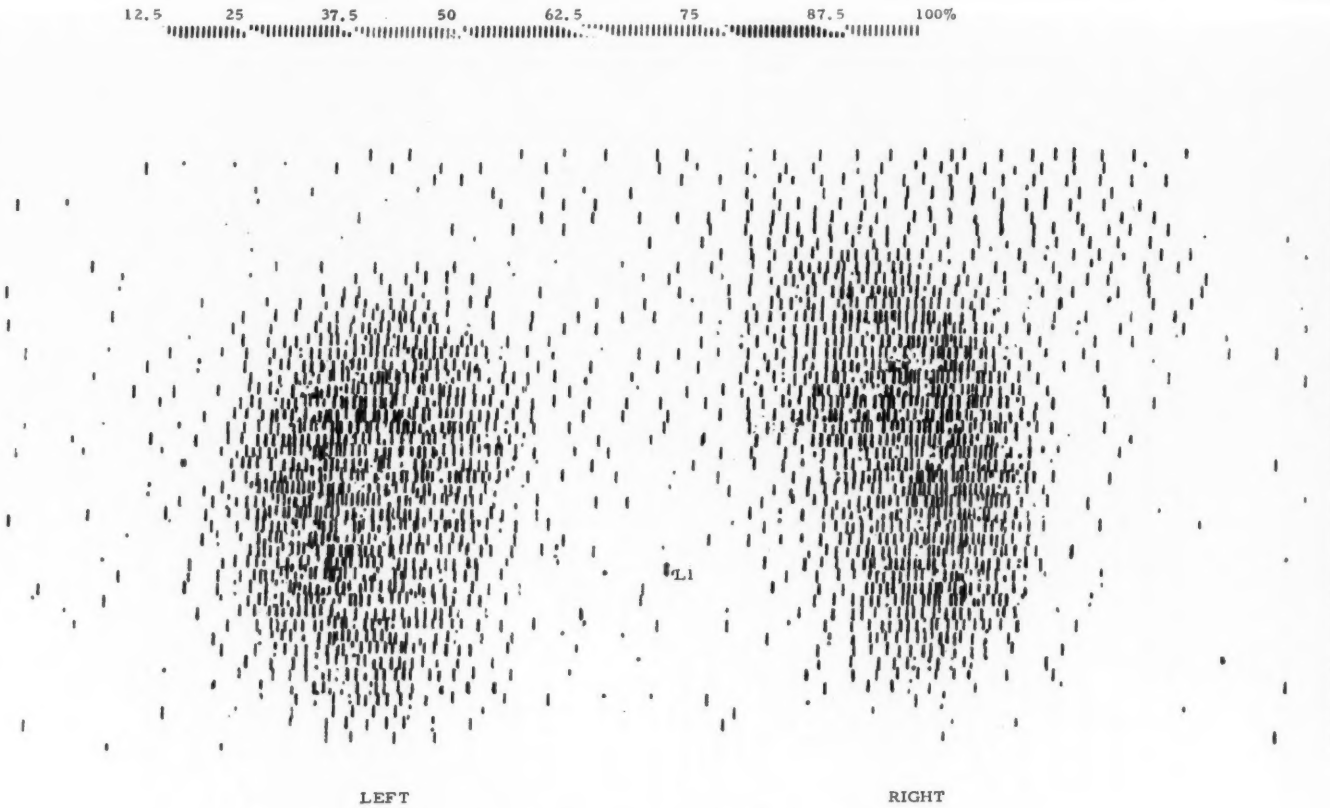

Fig. 3. Renal scan with a dose of 78 μc Hg^{203} Neohydrin. Scanning speed 6 mm per second; scale of 16 for printing. The increase in count-rate which is readily observed over the peripheral cortical area in the color print is less obvious in a black and white read-out.

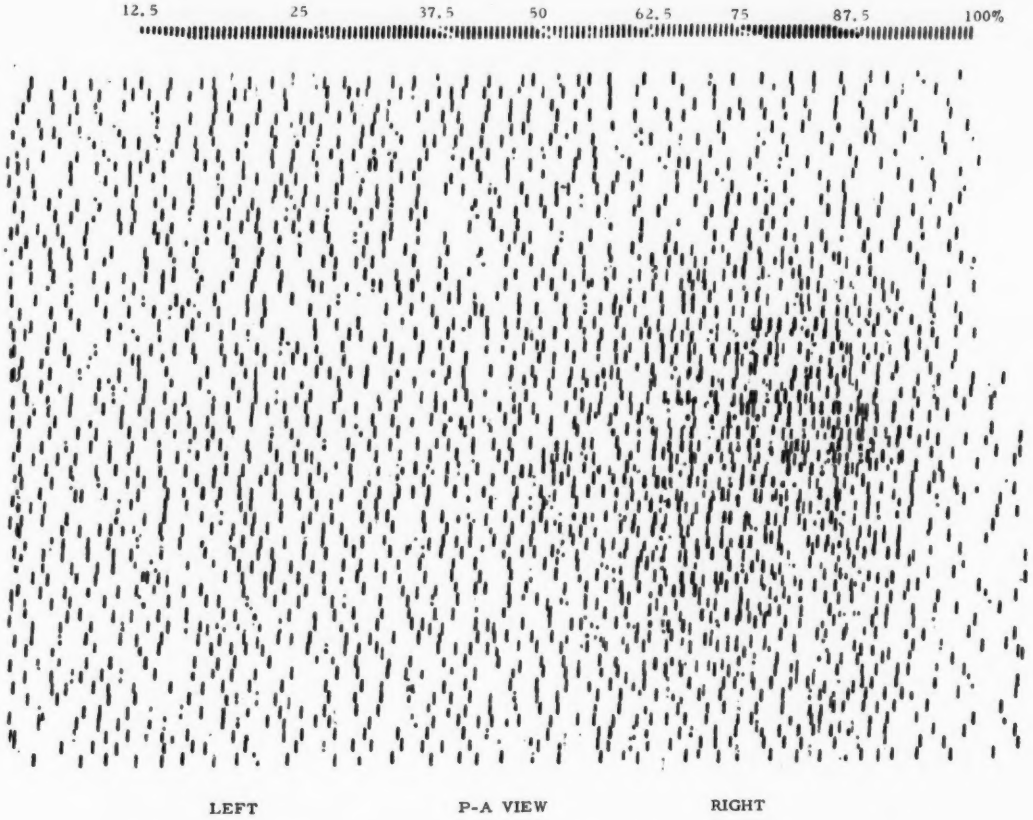

Fig. 4. Renal scan of a uremic patient with a dose of 70 μc Hg^{203} Neohydrin. Scanning speed 6 mm per second; scale of 8 for printing. On an intravenous pyelogram it was not possible to visualize either kidney. The color print outlines the right kidney.

a correspondingly higher scale factor. The choice of these two selections rarely causes any difficulty.

RESULTS

A few examples of color print-outs are shown in Figs. 1-4. In Figure 1 a color print of a thyroid is presented together with the black and white carbon copy which is always simultaneously obtained with the color print-out. Figure 2 is a color scan of a liver and Figures 3 and 4 that of the renal areas of one patient with two normal kidneys and of another patient with visualization of only one very poorly functioning kidney which would not be seen radiographically.

It is obvious that the color prints allow a quick estimate of the relative concentrations of the labeled material. If it can be assumed that the specific radioactivity (μc/gm) is constant within an organ, then a variation in the color can be taken as a measure of the variation of the organ thickness. Finally, lines can be drawn around areas of constant count-rate, which may yield additional information.

SUMMARY AND CONCLUSIONS

A simple method for color coding of radioisotope scans has been presented. A carriage moves 8 colored typewriter ribbons beneath the printing stylus so that the printing color changes with the count-rate. It should be possible to install this system in all types of scanners presently in use. The operation of the color-scan requires finding the approximate maximum count-rate. After completion of the scan the results are immediately available in their final form without further processing.

A change in color delineates clearly areas of different count-rate without losing any information due to a preselected cut-off level. This provides an unambiguous interpretation of the information contained in a radioisotope scan.

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JOURNAL OF NUCLEAR MEDICINE 4:446-452, 1963

Results of a Standardized Hippuran Renogram[1]

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Milwaukee, Wisconsin

INTRODUCTION

All renograms done in this hospital are evaluated by a normal range previously determined in a study of seventy-eight individuals with no evidence of kidney disease.[1] The results of the next two-hundred and fifty patients evaluated by this technique are presented.

MATERIALS AND METHODS

All studies were done using a Picker dual detection system.[2] Prior to study, the sensitivity of each detector was checked against a standard source for a constant and equal response. All patients were given 400 cc of water 20 minutes before the test. Originally, 10 drops of saturated potassium iodide solution was given for thyroid block but this proved unnecessary and was discontinued since it did not affect the 30-minute or the 24-hour Hippuran excretion.

A standardized dose of Hippuran selected for the renogram was 0.3μc per kg. One-tenth of this dose or 0.03μc per kg was first injected intravenously and the kidneys localized by moving the detectors to the areas of maximum activity over the back. This required less than five minutes and gave accurate localization. Following the kidney localization, 0.3μc per kg was injected and a 20-minute tracing obtained at a chart speed of 12 inches per hour with a sensitivity of 30,000 counts per minute full scale and a 1.5 second time constant. Thirty minutes after the last injection, a voided urine specimen was obtained and the fraction of Hippuran excreted was calculated.

The previously determined range of normal was plotted to illustrate the mean plus one and two standard deviations, Figure 1. A transparent photocopy of this plot was used as an overlay to evaluate each renogram. It was considered normal if the renogram fell within the plot and did not deviate markedly from

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[1]From the Radioisotope Service of the Wood Veterans Administration Center and the Department of Medicine, Marquette University School of Medicine, Milwaukee, Wisconsin.

[2]Picker X-Ray Corporation, White Plains, N. Y.

the normal contour. A few cases with outflow obstruction showed a secretory peak at the low range of normal and a 20-minute value near the upper limit of normal. This type of tracing was never obtained in the normal series and is due to poor emptying of the kidney. Any tracing which deviated upward more

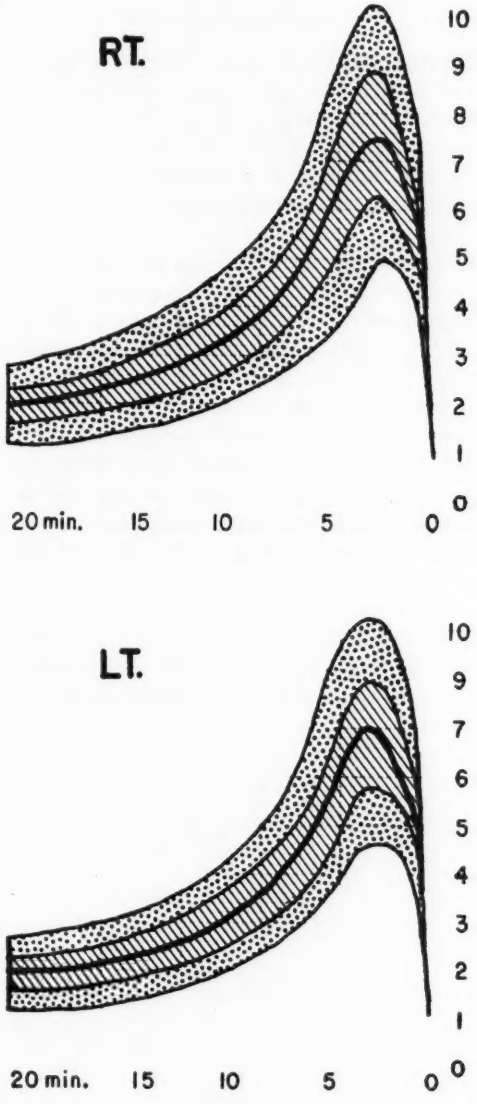

Fig. 1. Normal Range. Mean and 1 and 2 Standard Deviations.

than two standard deviations during the excretory phase was considered abnormal.

The thirty-minute Hippuran excretion was evaluated according to a previously determined normal. (1) This included a mean value of 67.1 ± 5.7 per cent. The two standard deviations lower limit of normal was therefore set at 56 per cent.

RESULTS AND DISCUSSION

There were 95 normal and 155 abnormal studies. A diagnosis of renal disease was made in eight of the patients with normal renograms, as follows: one minimal nephrosclerosis on kidney biopsy; three congenital malformations of the kidneys detected by excretory urogram; two mild chronic pyelonephritis; one acute pyelonephritis and one chronic membranous nephritis with the nephrotic syndrome. None of these patients demonstrated any renal functional impairment by other renal function tests.

The average of few laboratory studies in patients with normal renograms is shown in Table I. This was a relatively young group with average age of 39 years. Only four were over 52 years. The 30-minute Hippuran excretion averaged 65.2 per cent. This agrees with our previously established average of 67 per cent. The average BUN was 13 and none exceeded 20 mg per cent. The 15 minute PSP excretion averaged 39 per cent.

The abnormal laboratory values in the patients with normal renograms are summarized in Table II. Urine abnormalities were infrequent with pyuria (11 cases) and albuminuria (13 cases) the most common. The 30-minute Hippuran excretion fell below normal in only three cases and these were each 55 per cent. The PSP excretion was abnormal in four of 32 cases and the urea clearance in one of seven cases. The BUN never exceeded 20 mg per cent. The excretory urograms, retrograde urograms and renal biopsies were abnormal in 14 of 34 cases, four of seven cases and one of six cases respectively. The high incidence of abnormal urograms may have resulted from the consideration of "indistinct or poor visualization" as abnormal. Since this finding correlated so well with the

TABLE I

PATIENTS WITH NORMAL RENOGRAM

No. of Patients	*Mean Values*			
	Age	*30-Minute Hippuran Excretion*	*BUN mg.%*	*PSP % Excretion at 15 Minutes*
95	39 (22-64)	65.2 ±5.9	13	39

TABLE II

ABNORMAL STUDIES IN PATIENTS WITH NORMAL RENOGRAM

Total Patients	*Pyuria*	*Albuminuria*	*30-Min. Hippuran Excretion Below 56%*	*PSP 15 Min. Below 25%*	*Urea Clearance Below 70%*	*BUN Above 20 mg%*	*Excretory Urogram*	*Retrograde Urogram*	*Renal Biopsy*
95	11	13	3	4 of 32	1 of 7	0	14 of 34	4 of 7	1 of 6
Above Studies Contributed to Renal Disease Diagnoses									
	3	1					3		1

abnormal studies and is not a normal finding, it was considered a significant abnormality although recommended follow-up urograms often were not done. The main laboratory study contributing to the eight diagnoses of renal disease are shown at the bottom of this table.

It therefore appears that false normal renograms were obtained in eight of 95 cases for an accuracy of nearly 92 per cent. Since none of them exhibited any impairment of renal function, a normal renogram tracing could be expected. Except for ectopic kidneys, most of the congenital anomalies, without functional impairment, would have a normal renogram. The number of such cases added by urograms would largely depend upon the frequency of such defects. Four cases of renal pathology were added by urograms and biopsy. Many falsely abnormal urograms were obtained

Since the kidneys are localized prior to study ectopic kidneys are readily detected. Two cases of unilateral and one case of unsuspected bilateral pelvic kidneys have been discovered by this procedure (2).

One-hundred and fifty-five or 62 per cent of the patients had abnormal renograms. Many had several renograms. Of the 91 cases studied for hypertension, the percentage of abnormal renograms was about the same, 69 per cent.

Nine of the patients did not have other studies to support a diagnosis of renal disease. However, six of these for various reasons did not receive an adequate renal workup to exclude renal disease. In three cases, all other studies except the renogram were normal. In one, a prone renogram was normal and the 30-minute excretion was normal. In the other two, the prone renogram was abnormal. If one assumes all of these nine patients to be free of renal disease, the accuracy of the abnormal renogram would be 94 per cent.

Normal studies in patients with abnormal renograms are shown in Table III. A normal 30-minute Hippuran excretion was associated with an abnormal renogram in 24 cases, 15 per cent. In each of these cases, the BUN was normal and the PSP and urea clearance when done, were normal. The frequency of other normal studies associated with an abnormal renogram included PSP 43 per cent, BUN 46 per cent, urea clearance 48 per cent, excretory urograms 20 per cent and renal biopsies 20 per cent. Abnormal findings were noted in less than 50 per cent of aortograms.

TABLE III

NORMAL STUDIES IN PATIENTS WITH ABNORMAL RENOGRAM

Type of Study	*No. of Studies*	*% Normal*
30-Minute Hippuran Excretion (above 56%)	155	15
PSP-15 min. Excretion (above 25%)	98	43
Blood Urea Nitrogen (below 20 mg.%)	124	46
Urea Clearance (above 70%)	46	48
Excretory Urogram	120	20
Renal Biopsy	35	20

Special attention was given to the cases with a unilateral abnormal renogram, exclusive of carcinoma, congenital absence, nephrectomy and nephrolithiasis. A summary of some of the findings in these cases is shown in Table IV. The unilateral abnormality was confirmed by excretory urogram in most cases. Although hypertension was a common finding, patient AR is the only one of the group who has had surgery and he has been normotensive 15 months postoperatively. Of 91 patients referred for hypertension, six had a unilateral abnormal renogram. The cases diagnosed by biopsy, nephrosclerosis and glomerulosclerosis, may be assumed to have bilateral disease, but it is of interest that the biopsy confirmed pathology only in the kidney which had the abnormal renogram.

TABLE IV.

CASES WITH UNILATERAL ABNORMAL RENOGRAM

Patient	*Age*	*B.P.*	*Abnormal Kidney*	*Supporting Evidence*
W.B.	65	144/90	Right	I.V.P.....Non-visualization Rt. Kidney Retrograde..Small Rt. kidney with pyelectasia
P.H.	29	120/80	Right (Obstruction)	I.V.P.....Obstruction at U-P junction
A.S.	50	230/120	Right	I.V.P.....Calcified cyst Rt. kidney
C.T.	29	136/96	Right	I.V.P.....Small Rt. kidney, poorly visualized Biopsy.....Rt. nephrosclerosis
J.W.	52	128/70	Right	I.V.P.....Nephroptosis and pyelectasia Rt. kidney
A.R.	51	162/130	Left	I.V.P.....Non-function Lt. kidney Subsequent nephrectomy—Hydronephrotic Lt. kidney. Normotension 15 months post-op.
J.R.	61	210/112	Left	I.V.P.....Non-visualization of Lt. kidney Aortography.Occlusion Lt. renal artery
E.B.	65	280/140	Right	I.V.P.....Smaller sized Rt. kidney Hg^{203} Scan...Absent lower pole Rt. kidney Aortography.Partial occlusion Rt. renal artery
F.C.	33	160/110	Right	Biopsy.....Nephrosclerosis Rt. Normal Lt.
D.B.	26	130/80	Right	Biopsy.....Glomerulosclerosis Rt. Normal Lt.

SUMMARY

The renograms of 250 patients have been evaluated according to a previously determined range of normal plot. The renogram was classified as normal if it fell within the two standard deviation range. Patients with a normal renogram had no detectable renal abnormality in over 90 per cent of the cases. An abnormal renogram was associated with other evidence of renal pathology in all but nine of 155 patients. The 30-minute excretion of Hippuran is less sensitive than the renogram. When used as a screening test for kidney disease, the Hippuran renogram appears to be the most accurate single test. The authors feel that this accuracy can only be obtained with a standardized procedure.

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Announcement to Authors
Preliminary Notes

Space will be reserved in each issue of THE JOURNAL OF NUCLEAR MEDICINE for the publication of one preliminary note concerning new original work that is an important contribution in Nuclear Medicine.

Selection of the preliminary note shall be on a competitive basis for each issue. One will be selected after careful screening and review by the Editors. Those not selected will be returned immediately to the authors without criticism. Authors may resubmit a rejected or revised preliminary note for consideration for publication in a later issue. The subject material of all rejected manuscripts will be considered confidential.

The text of the manuscript should not exceed 1200 words. Either two illustrations, two tables, or one illustration and one table will be permitted. An additional 400 words of text may be substituted if no tables or illustrations are required. Only the minimum number of references should be cited.

Manuscripts should be mailed to the Editor, Dr. George E. Thoma, St. Louis University Hospital, 1325 South Grand Blvd., St. Louis 4, Missouri. They must be received before the first day of the month preceding the publication month of the next issue, e.g., preliminary notes to be considered for the January, 1964 issue must be in the hands of the Editor before December 1, 1963.

JOURNAL OF NUCLEAR MEDICINE 4:453-461, 1963

Tagged Isomers and Analogues of Thyroxine (Their Transmission Across The Human Placenta and Other Studies)

John E. Kearns, M.D., and William Hutson, M.D.[1]

Evanston, Illinois

In an attempt to explain the increase in protein bound iodine, butanol extractable iodine, and I^{131} retention in the thyroid of the newborn, studies were made of the transmission of thyroxine; its analogues and isomers through the placental membrane. A review of the literature showed few references to this either in animals or humans. Villee (9), in his text on the placenta, made no reference. The most recent of scant work in animals (5) was in rats and showed little transfer of thyroxine. Grumbach and Werner (2) reported a small amount of levo-thyroxine in cord blood, and that it increased with the longer time lapse between doses and delivery. They found only a small amount of L-triiodothyronine in the cord blood. They calculated results as S.P.I.^{131} ratio.

The drugs L-thyroxine, D-thyroxine, L-triiodothyronine and D-triiodothyronine were checked for purity by the manufacturer and pharmaceutical houses which furnished them. The patient dose in each instance was 50 microcuries. Labor was induced at term in all 12 women. The various tagged substances were given 2 to 8 hours before delivery. Some of the patients were given iodide before the tagged drug. Neither time nor iodide affected the transfer. Equal samples of blood were taken from the mother and the umbilical cord at the time of delivery. A well counter was used to measure the activity and whole blood and serum were both counted. To express the difference in transfer of the tagged drugs, counts of cord blood are expressed as per cent of the mother's blood. To have a control of I^{131}, 50 microcuries were given 2 hours before delivery. There were equal counts in mother's and cord blood (100% transfer). In the instance of L-thyroxine, there was 5 per cent of tagged drug in cord blood. Similarly, D-thyroxine had 9 per cent in the cord blood. When L-triiodothyronine and D-triiodothyronine were tested, there was 25 per cent in the cord blood. Paper chromatography (developed in tertiary amyl alcohol saturated with 2N sodium hydroxide) was used in each instance to see if the tagged drug given was coming through unchanged. The isomers were the same in all instances except one, although the quantity of radioactivity was small. (Fig. 1b)

[1]From the Department of Surgery and Radiology, Evanston Hospital and Northwestern University Medical School, Evanston, Illinois.

GROUP II—NEWBORN INFANTS

Name	*Sex*	*Age*	I^{131}	*PBI*	*BMR*	*Bone Age*
Ho	M	4 hours	100%	7.5	—	Newborn
Ra	F	1 day	88%	7.4	—	Newborn
Tr	M	1 day	96%	4.7	—	Newborn
Cr	M	1 day	100%	11.3	—	Newborn
Be	F	1 day	66%	10.0	—	1 month
Za	F	1 day	99%	9.5	—	3 months
We	M	1 day	74%	11.0	—	Newborn
Sp	M	1 day	56%	11.5	—	Newborn
St	F	2 days	72%	10.5	—	Newborn
Bu	M	2 days	37%	12.5	—	1-2 months
Ne	F	2 days	76%	11.5	—	Newborn
Vo	F	2 days	100%	9.2	—	Newborn
Me	F	2 days	69%	7.2	—	1-2 months
Ti	F	2 days	30%	9.9	—	Newborn
Pa	F	3 days	65%	11.0	—	1-2 months
Jo	M	3 days	90%	9.5	—	Newborn
Bo	M	3 days	58%	5.9	—	Newborn
Ma	F	3 days	73%	9.9	—	Newborn
Fr	F	3 days	75%	9.3	—	Newborn

Average Infant
2 days old
I^{131}–75% (30%–100%)
PBI–9.4(4.7–11.5)
Bone Age—Newborn

Fig. 1. a. This chart shows P.B.I.s and I^{131} uptake in newborns.

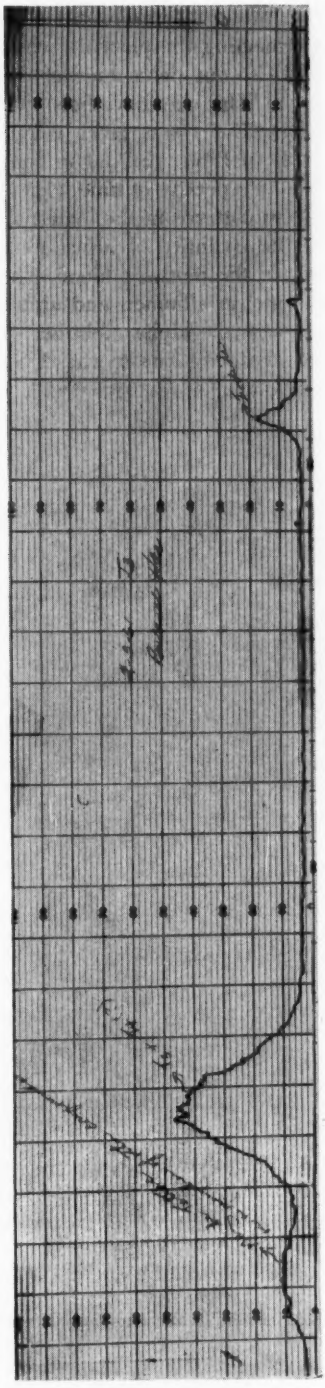

Figure 1b. Chromatograph showing contamination.

Our results differed from those of Grumbach (2) because we found no increase in amount of drug permeating the placenta when it had been given at a greater time before delivery. Also our percentage of dextro and levo-triiodothyronine was higher in cord blood. This may have been due to the different method of administration of the drugs. Theirs was given intravenously while ours was administered orally. Our study of P.B.I. (S.P.I.) in cord and maternal blood at birth showed them to be equal irrespective of time. (Fig. Ic)

The electrophoretic protein patterns in the maternal and cord blood showed a great difference between the quantity of alpha globulin fractions; it being lower in the cord blood than in the mother's blood. The largest amount of thyroxine binding factor was found in albumen and alpha globulin fractions (7). The highest concentration was in the alpha globulins. The lack of transmission of these tagged drugs may have been due to the difference in these fractions. (Figs. 2) In a previous publication (4) we reported, as have others that during

GROUP I—MOTHERS AT TERM AND THEIR INFANTS

Mother	*Age*	*P.B.I. at Delivery*	*Newborn*	*Sex*	*P.B.I. Cord Blood*	*Wt. (lbs.)*
De	26	8.7	De	F	8.0	$9\frac{5}{}$
He	26	7.0	He	F	7.3	$7\frac{3}{}$
Ki	23	7.5	Ki	M	7.8	$7\frac{3}{}$
Me	34	7.9	Me	M	7.8	$7\frac{14}{}$
Pe	21	7.8	Pe	M	7.8	$8\frac{3}{}$
Ra	25	7.1	Ra	F	7.8	$8\frac{5}{}$
Sn	26	12.2	Sn	F	6.3	$7\frac{8}{}$
Sw	32	10.5	Sw	F	8.0	$7\frac{3}{}$
Te	31	5.0	Te	M	6.7	$7\frac{8}{}$
Wa	39	7.5	Wa	M	8.0	$7\frac{9}{}$

Figure 1. c. Chart showing P.B.I.s of mother and newborn at delivery.

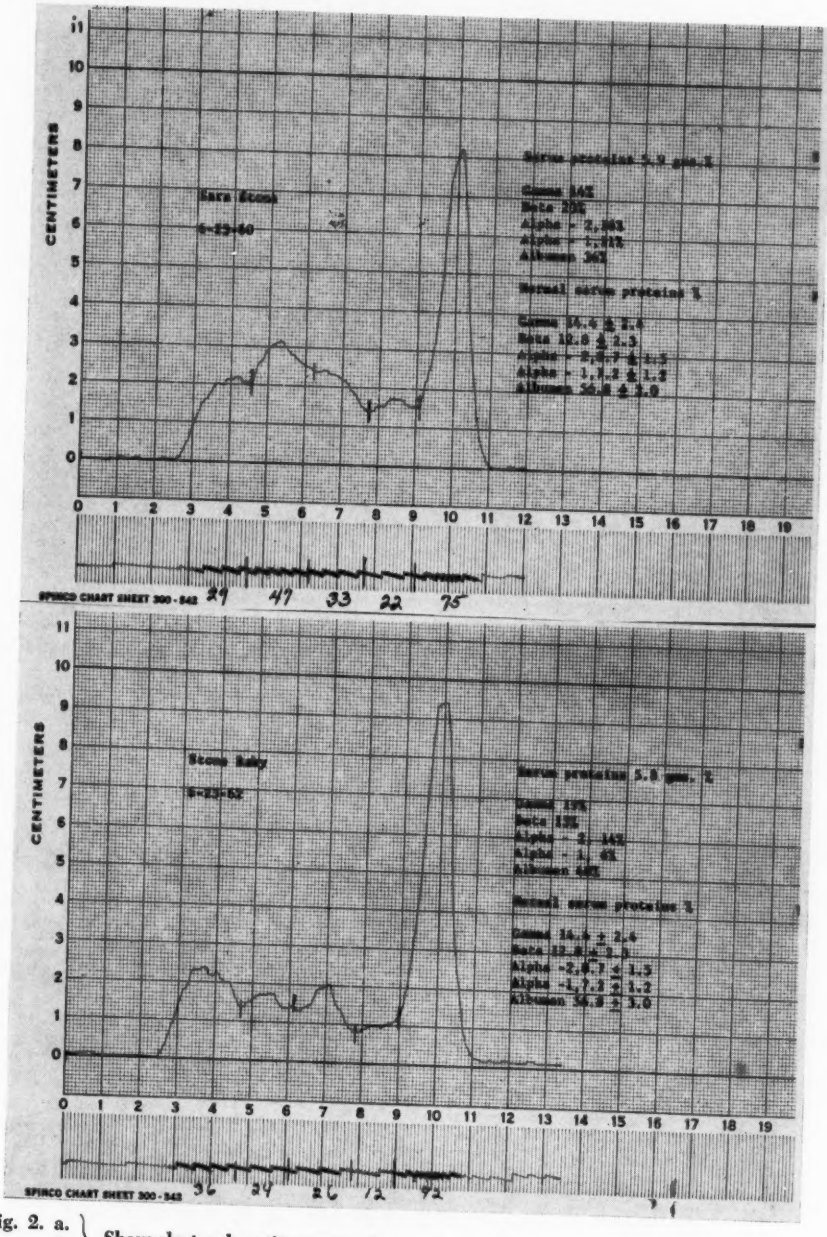

Fig. 2. a. } Show electrophoretic patterns for mother and her newborn.
b. }

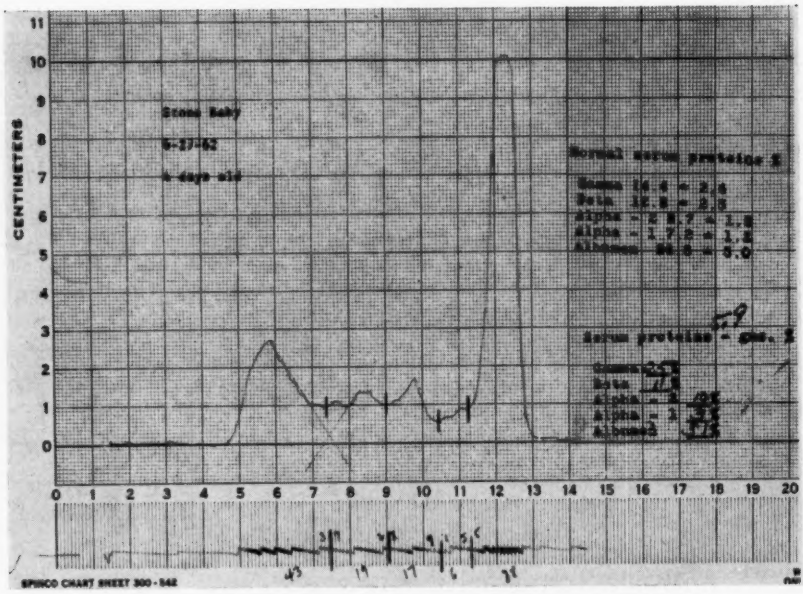

Figure 2. c. Show electrophoretic patterns for mother and her newborn.

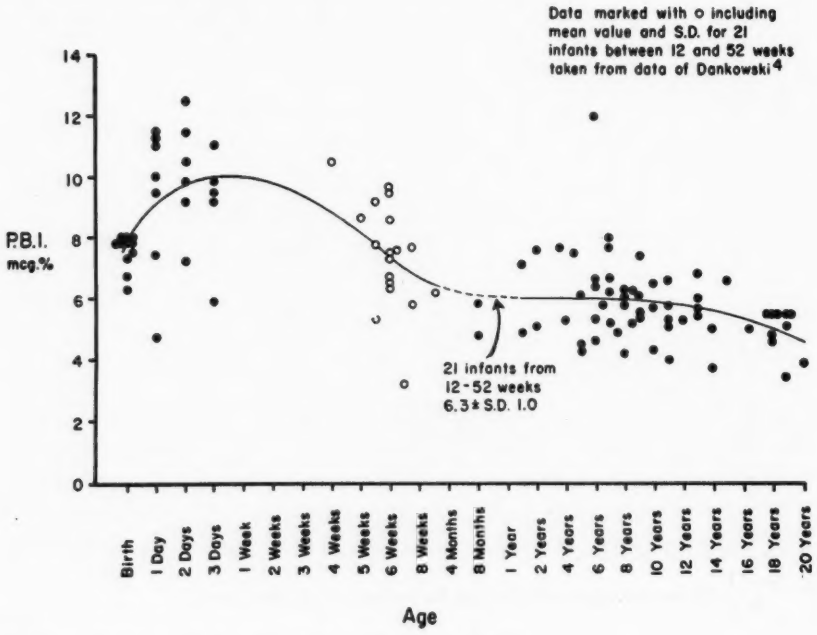

Fig. 3. a. Scattergraph showing P.B.I.s with age in children.

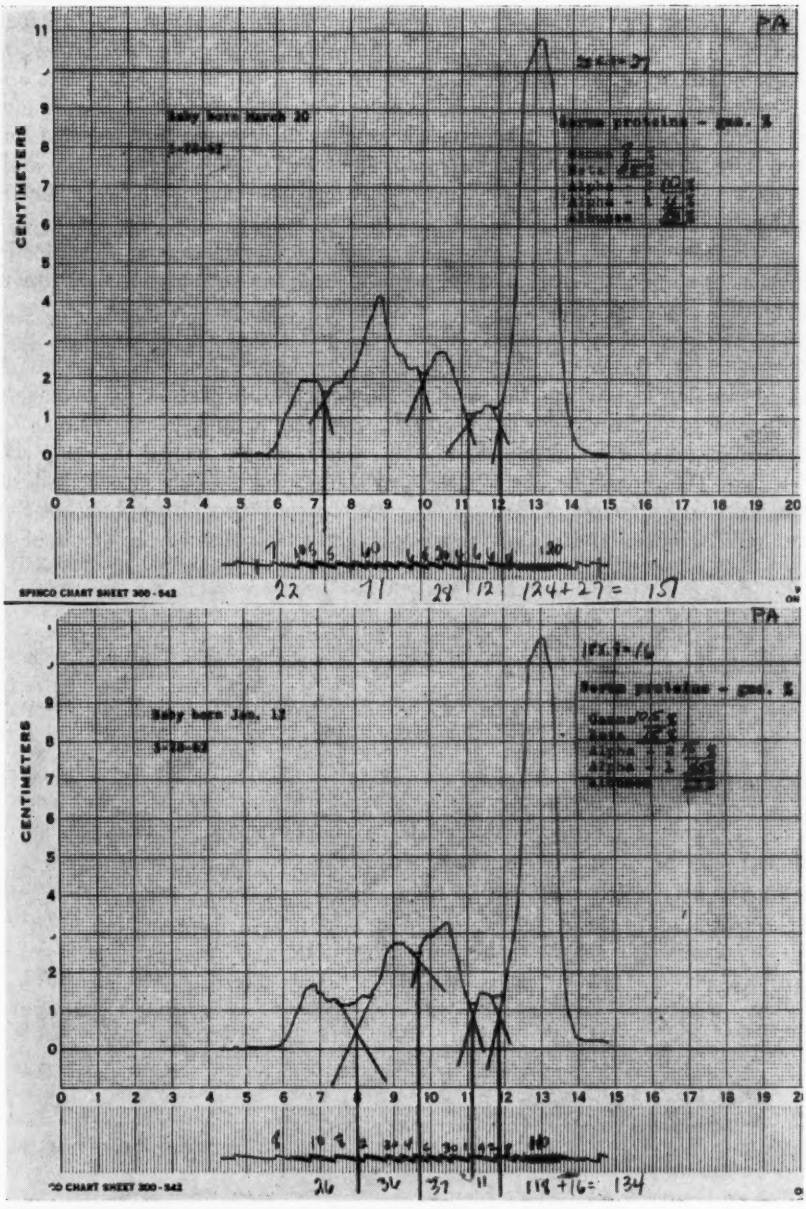

Figure 3b. Electrophoretic pattern in 2 month old infant.

c. Electrophoretic pattern in 4 month old infant.

the first, second, and third days of life, the protein bound iodine, as well as the butanol extractable iodine, were at extremely high levels. (Fig. 3a) We found that the alpha globulin was low at that time in the newborn and continued so at least until the fourth month. (Fig. 3b&c)

Since tagged drugs were available, 10 people over 50 years of age were given 50 microcurie doses and 24 hour uptake studies were made to determine body area distribution. These were similar to those of Tapley (3) in rats. Giving iodide to patients did not effect collection of thyroxine but made T^3 behave like thyroxine. This may have been due to trapping by T^3 making it T^4. (Fig. 4)

Chaikoff (8) was one of the first to study the excretion of thyroxine-like substances from the biliary system. Keating (1) has shown that they are not truly thyroxine but some analogue or hydroxide. Bile drainage of the tagged drugs was studied in 3 patients. It was collected over a 12 hour period after a dosage of 50 microcuries. The collections were made through "T" tubes and blood samples were taken at the end of 12 hours. In this instance the average secretion of tagged drug was 38 per cent. A patient with a jejunal fistulae was studied in a similar manner and only 10 per cent of the tagged materials were detected. There were no special chemical studies made of these collected substances. Large amounts of these drugs were excreted through the bile but there was rapid absorption and only small amounts were noted in the stools of patients (6).

% Distributing in Living Humans

	LT^4	DT^4	LT^3	DT^3	DT^3+I^{127}
HEAD	6.3	3.7	4.5	6.5	4.3
THYROID	24.7	41	63	60	17.2
HEART	15.1	10.6	7.3	7.5	15.4
LIVER	34.9	30	11.2	13.3	30
BLADDER	12.5	7.6	8.9	8.3	21.8
HAND	6.5	6.4	5.3	4.4	6.3

Figure 4. Shows per cent of drugs in body compartments in humans.

CONCLUSION

Some physiological properties of tagged isomeres and analogues of thyroxine are reported:

1. They are decreased in cord blood although there is complete transmission of Na I^{131}.
2. There seems to be a specific distributional difference between thyroxine and triiodothyronine in its collections in body areas.
3. Excretion in bile and rapid re-absorption in the gut are shown.

ACKNOWLEDGEMENT

We wish to thank Drs. E. Seymour Burge and Buel Morley for their assistance. Drugs were furnished by Baxter Laboratories, Morton Grove, Illinois and Smith, Kline and French, Philadelphia, Pa.

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A Digital-Computer Method for Rapid Radioactivity Calculations

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Kalamazoo, Michigan

INTRODUCTION

The development of liquid scintillation counters capable of handling large numbers of samples automatically has reduced substantially the technical difficulties of counting radioactive samples of weak beta-emitting isotopes. Since a single physiological-disposition study with an isotope-labeled drug may yield hundreds of samples, several days of additional mathematical calculations are required. Although electronic computers, such as the IBM 1620 Digital Computer, are used most frequently for more difficult mathematics, we have found it convenient to use this instrument as a labor-saving device in calculating data from radioactive samples. With the economies of time effected with this technique, it becomes possible to divert a significantly greater portion of laboratory effort back to nonroutine research operations.

EXPERIMENTAL

Types of Problems Encountered

In any detection device used for radioactivity measurements, counting efficiency is less than 100 per cent because of factors such as geometry of the sample and detector. In liquid scintillation counters losses in efficiency also may occur because of color- or solute-induced quenching. An additional variable encountered is that of aliquot size. Thus, there are four general problems introduced by constant or variable quenching and constant or variable aliquot to total sample relationships. The IBM 1620 Computer programs (1)[2] designed specifically for these problems are as follows:

Program	*Quenching*	*Total Sample Aliquot*
1A	Constant	Constant
1B	Constant	Variable
2A	Variable	Constant
2B	Variable	Variable

[1]From the Biochemical Research Division, The Upjohn Company, Kalamazoo, Michigan.

[2]In order to save Journal space, copies of the computer programs are not given here; however, they may be obtained from the authors on request.

Sample Problems and Solutions

The definition of constants and variables employed in the programs described are shown in Table I. In Table II are listed typical data for three samples for which Programs 1A or 1B would be employed. In order to calculate the percent recovery (RECOV) of the original radioactive dose in each sample, Equation 1 below is used.

$$\left(\frac{\text{CTS}}{\text{TIME}} - \boxed{\text{BKG}}\right) \times \underset{\text{CPM}}{\boxed{\text{SF}}} \times \underset{\text{CPMT}}{\boxed{\text{VTVA}}} \times \frac{1}{\boxed{\text{EFREL}}} \times \underset{\text{CPMQ}}{\frac{1}{\boxed{\text{EFABS}}}} \times \underset{\text{DPMT}}{\frac{100\%}{\boxed{\text{TOTAL}}}} = \text{RECOV} \qquad (1)$$

In the above equation all the terms enclosed in a solid box are data constants. The unenclosed terms are data variables or computed variables. When VTVA is a constant, Program 1A is used. If VTVA is a computed variable, separate values of VA and VT are used for each sample, and Program 1B is employed. The IBM 1620 print outs for both programs are shown in Figures 1 and 2. It will be noted that the input to the computer consists of the data constants followed by the data variables. These values then are printed out in the same sequence, followed by the computed variables.

In Table III are listed typical data for which Programs 2A or 2B would be used. These programs are based on Equation 2 below.

$$\left(\frac{\text{CTS}}{\text{TIME}} - \boxed{\text{BKG}}\right) \times \underset{\text{CPM}}{\boxed{\text{SF}}} \times \underset{\text{CPMT}}{\boxed{\text{VTVA}}} \times \frac{\boxed{\text{CPMST}}}{\left[\left(\frac{\text{CTSX}}{\text{TIMEX}} - \boxed{\text{BKG}}\right) - \underset{\text{CPMX}}{\text{CPM}}\right]} \times \underset{\text{CPMQ}}{\frac{1}{\boxed{\text{EFABS}}}} \times \underset{\text{DPMT}}{\frac{100\%}{\boxed{\text{TOTAL}}}} = \text{RECOV} \qquad (2)$$

XDIF

EFREL

Equations 1 and 2 are identical except that in the former EFREL was a data constant, while in the latter EFREL is a varable computed from the terms CPMST, CTSX, TIMEX, and CPM. As in Equation 1, the terms in Equation 2 enclosed in a solid box are data constants, and those unenclosed are data variables or computed variables. In analogy to Programs 1A and 1B, Program 2A is used when VTVA is a data constant, while Program 2B is used with VTVA as a computed variable. The print outs for Programs 2A and 2B are shown in Figures 3 and 4.

It should be emphasized that the data listed in Tables II and III are hypothetical data for only three samples. The programs referred to in this report actually will accommodate an infinite number of samples. Replicate samples or replicate counting of samples are handled as separate entries. Although it is possible to program the computer to calculate the mean of replicates or replicate counts, this was not done since the number of replicates frequently may vary within a given group of samples (except in specialized or routinized studies) and additional coded instructions on the data input tape would be required.

DISCUSSION

Although the programs described above were designed for a specific type of problem, namely calculation of drug-distribution data, the actual mathematical equations employed are quite general. Thus, in any case where a radioactive material is distributed in a multi-component system, such as an animal or a fractionation process, the programs may be applied. This is accomplished simply by assigning a different meaning to a given constant or variable, of, if preferred, by changing the designation of constants or variables in the computer program. Routine use of these programs in our Laboratories has indicated that almost any tracer experiment lends itself to automatic computation techniques based on the programs described here and that the number of samples to be calculated usually determines whether the computer is used.

The problems cited above were solved for RECOV (see Table I), expressed as percent of administered dose; however, certain problems by their nature cannot be solved for this term but for some other value such as CPMT or DPMT.

TABLE I

DEFINITION OF CONSTANTS AND VARIABLES

1. BKG–(C)–Counts/minute (cpm) of sample vial containing counting solution but without sample.
2. CPM–(V)–Cpm of sample corrected for BKG.
3. CPMST–(C)–Cpm of internal standard corrected for BKG.
4. CPMQ–(V)–CPM corrected for SF, VTVA, and EFREL.
5. CPMT–(V)–CPM corrected for SF and VTVA.
6. CPMX–(V)–Cpm of sample plus added internal standard.
7. CTS–(V)–Counts recorded by counter for any given sample.
8. CTSX–(V)–Counts recorded by counter for any given sample to which internal standard was added.
9. DPMT–(V)–CPM corrected for SF, VTVA, EFREL, and EFABS.
10. EFABS–(C)–Absolute counting efficiency of machine, *i.e.*, observed counts/actual disintegrations under conditions of no quenching.
11. EFREL–(C, V)–Relative counting efficiency, *i.e.*, quenched counts/unquenched counts.
12. RECOV–(V)–Percent of dose (or total dpm) represented by any given sample.
13. SF–(C)–A sampling factor constant used to simplify values of VA or VTVA.
14. TIME–(V)–Time recorded by counter for any given sample.
15. TIMEX–(V)–Time recorded by counter for any given sample to which internal standard was added.
16. VA–(V)–Aliquot volume (or weight); actually the sample which was counted.
17. VT–(V)–Total volume (or weight) from which VA was taken.
18. VTVA–(C, V)–VT/VA.
19. XDIF–(V)–CPMX minus CPM, *i.e.*, observed cpm of internal standard counted in presence of sample.

(C) = Constant, (V) = Variable, (C, V) = Constant or Variable

TABLE II

SAMPLE DATA FOR PROGRAMS 1A AND 1B

TABLE II

SAMPLE DATA FOR PROGRAMS 1A AND 1B

Data Constants		*Program*	*Data Variables*				*Program*
				Sample No.			
				1	*2*	*3*	
BKG	30.0	1A and 1B	TIME	5.00	10.0	15.0	1A and 1B
EFREL	85.0%	1A and 1B	CTS	1.00×10^4	1.00×10^4	1.00×10^4	1A and 1B
EFABS	65.0%	1A and 1B	VA	0.100	0.100	0.100	1B
VTVA	50.0	1A	VT	30.0	35.0	40.0	1B
SF	3.33	1A and 1B					
TOTAL	4.50×10^7	1A and 1B					

TABLE III

SAMPLE DATA FOR PROGRAMS 2A and 2B

Data Constants		*Program*	*Data Variables*				*Program*
				Sample No.			
				1	*2*	*3*	
BKG	30.0	2A and 2B	TIME	5.00	10.0	15.0	2A and 2B
CPMST	2.00×10^3	2A and 2B	CTS	1.00×10^4	1.00×10^4	1.00×10^4	2A and 2B
EFABS	65.0%	2A and 2B	TIMEX	3.10	4.20	5.30	2A and 2B
VTVA	50.0	2A	CTSX	1.00×10^4	1.00×10^4	1.00×10^4	2A and 2B
SF	3.33	2A and 2B	VA	0.100	0.100	0.100	2B
TOTAL	4.50×10^7	2A and 2B	VT	30.0	35.0	40.0	2B

IBM 1620 PRINT OUT, PROGRAM 1A

BKG	30.0000
EFREL	.8500
EFABS	.6500
VTVA	50.0000
SF	3.3300
TOTAL	45000000.0000

TIME	CTS
5.00	10000.00
10.00	10000.00
15.00	10000.00

CPM	CPMT	CPMQ	DPMT	RECOV
1970.0	328005.0	385888.2	593674.2	1.319276000
970.0	161505.0	190005.8	292316.7	.649592730
636.6	106005.0	124711.7	191864.2	.426364970

(Fig. 1)

Alternatively, no logical value for SF may exist. In these cases proper selection of program and substitution of unity (or other suitable value) for various constants will allow a high degree of flexibility. For example, if the final answer desired is DPMT, the value of 100 is assigned the constant, TOTAL, and the last two variables, DPMT and RECOV, are equivalent. Additionally, if TOTAL = dpm per microgram drug $\times 100$, then the units of RECOV are micrograms drug per sample, or micrograms drug per ml when VT = 1.0 ml. Numerous other variations are possible by appropriate assignment of units to the proper constant or vari-

IBM 1620 PRINT OUT, PROGRAM 1B

BKG	30.0000
EFREL	.8500
EFABS	.6500
SF	3.3300
TOTAL	45000000.0000

TIME	CTS	VA	VT	VTVA
5.00	10000.00	.1000	30.0000	300.0000
10.00	10000.00	.1000	35.0000	350.0000
15.00	10000.00	.1000	40.0000	400.0000

CPM	CPMT	CPMQ	DPMT	RECOV
1970.0	1968030.0	2315329.4	3562045.2	7.915655900
970.0	1130535.0	1330041.1	2046217.0	4.547148800
636.6	848040.0	997694.1	1534914.0	3.410920000

(Fig. 2)

IBM 1620 PRINT OUT, PROGRAM 2A

BKG	30.0000	VTVA	50.0000
CPMST	2000.0000	SF	3.3300
EFABS	.6500	TOTAL	45000000.0000

TIME	CTS	TIMEX	CTSX
5.00	10000.00	3.10	10000.00
10.00	10000.00	4.20	10000.00
15.00	10000.00	5.30	10000.00
CPM	CPMX	XDIFF	EFREL
1970.0	3195.8	1225.8	.612903200
970.0	2350.9	1380.9	.690476150
636.6	1856.7	1220.1	.610062900
CPMT	CPMQ	DPMT	RECOV
328005.0	535166.0	823332.4	1.829627500
161505.0	233903.8	359852.0	.799671110
106005.0	173760.7	267324.2	.594053910

(Fig. 3)

IBM 1620 PRINT OUT, PROGRAM 2B

BKG	30.0000		
CPMST	2000.0000	SF	3.3300
EFABS	.6500	TOTAL	45000000.0000

TIME	CTS	TIMEX	CTSX
VA	VT	VTVA	
5.00	10000.00	3.10	10000.00
.1000	30.0000	300.0000	
10.00	10000.00	4.20	10000.00
.1000	35.0000	350.0000	
15.00	10000.00	5.30	10000.00
.1000	40.0000	400.0000	
CPM	CPMX	XDIFF	EFREL
1970.0	3195.8	1225.8	.612903200
970.0	2350.9	1380.9	.690476150
636.6	1856.7	1220.1	.610062900
CPMT	CPMQ	DPMT	RECOV
1968030.0	3210996.4	4939994.4	10.977765000
1130535.0	1637326.6	2518964.0	5.597697700
848039.9	1390086.1	2138594.0	4.752431100

(Fig. 4)

able. The only restriction to use of existing programs is that whenever the program calls for a numerical value of a data constant or data variable, some value other than zero must be assigned; the space may not be left blank. Similarly, the computer always will print the same number of variables per sample (*i.e.*, 7 for 1A; 10 for 1B; 12 for 2A; 15 for 2B).

Although counts per minute can be converted to disintegrations per minute in a single step whether or not quenching exists, it is of interest in certain experiments to know the degree of quenching produced by each sample. Thus, the term EFREL (relative counting efficiency) has been included in the computations and is obtained directly rather than by conventional means.

Although it is not necessary that all data entered into the computer be printed out, it is convenient to do so and also to print out all major computations. If the raw data are reconciled with the data-tape print out, then the only record which must be retained is the computer print out. This will contain the original data plus computations in a legible columnated format, which may be filed conveniently. Additionally, it affords ready access to any stage of computation of all samples for comparison or for use of intermediate data in alternate calculations.

It is possible to combine all four programs into a single master program. However, the programs were kept simple for operational expediency, since personnel frequently are utilized who have little or no background with computer or tracer technology. The present programs require only that the operator be able to prepare the data tape via the Friden Flexowriter and to follow a series of fixed instructions for use of the computer.

Although the programs described in this report are designed specifically for the IBM 1620 Digital Computer, other computing systems may be utilized with appropriate programming, such as the Burroughs 101E system used earlier in our Laboratories. Since many computing systems accept a punched tape input, and since the preparation of the data tape consumes about one-half of the total time required to convert raw data to final results, addition of a punched-tape, read-out accessory to the counter becomes an important consideration. This tape would contain the data variables TIME and CTS as well as TIMEX and CTSX. Thus, neglecting the five or six data constants required, the counter read-out would provide all data variables for Programs 1A and 2A, one-half those of Program 1B, and two-thirds those of Program 2B. Without this accessory, however, the procedure as reported effects a time saving of approximately 90 percent.

REFERENCE

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The Bromide Space After the Intravenous Administration of ^{82}Br.[1,2]

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London, England.

INTRODUCTION

The volume of distribution of bromide or its isotopes in the human has been used as a measure of the extracellular fluid volume, the method being based on the assumption that bromide is distributed similarly to chloride (1) and that the latter ion is confined to the extracellular fluid. ^{82}Br, with its relatively short half life (36 hours) is the most convenient isotope but its use presents certain difficulties because bromide is not distributed in precisely the same fashion as chloride. The concentration of bromide in the normal cerebrospinal fluid is lower than would be expected from its chloride content, but bromide is selectively concentrated in the red blood corpuscles (1). The potential error caused by its low concentration in the cerebro-spinal fluid is so small that it can be ignored but a correction factor must be applied to allow for the high concentration in the red cells (2).

In addition it has been shown that the concentration of bromide in the gastric contents is up to 4-6 times as great as would be expected from the chloride content (3). This selective concentration of ^{82}Br in the gastric contents and mucosa has also been demonstrated in the experimental animal (4) but its quantitative effect on the measurement of the bromide space is not known.

The present study was undertaken to assess the volume of distribution of ^{82}Br in humans when given intravenously and to find out what effect the high concentration of ^{82}Br in the gastric contents has on this bromide space.

MATERIALS & METHODS

The ^{82}Br was prepared as KBr in sterile solution. The ^{42}K content of this solution was negligible even immediately after irradiation of the target compound and its concentration rapidly decreased relative to that of ^{82}Br with the

[1]Department of Surgical Studies and the Institute of Nuclear Medicine.

[2]The Middlesex Hospital.

The KBr was supplied by the Radiochemical Centre, Amersham, U.K.

TABLE I

TIME OF EQUILIBRATION OF EXTRACELLULAR VOLUME

Patient	*2 Hour Volume in Litres*	*Percentage of 12 Hour Value*	*4 Hour Volume in Litres*	*Percentage of 12 Hour Value*	*6 Hour Volume in Litres*	*Percentage of 12 Hour Value*	*12 Hour Volume in Litres*
4	19.9	100	19.9	100	20.2	100.5	19.9
5	16.9	99.5	16.9	99.5	16.6	98	17.0
6	14.5	95	15.0	98	14.4	94.5	15.3
7	15.62	102	15.0	98.5	15.8	103	15.3
8	10.95	102	11.03	103	11.10	103.5	10.75
35	15.2	102	15.4	104	14.8	100	14 8

passage of time; γ-counters insensitive to ^{42}K were used for all radio-assays. A dose between 10 and 12 microcuries of ^{82}Br in approximately 2 mgm stable Br was injected intravenously, the patient having fasted for the preceding 2 hours and having just emptied the bladder. The amount of solution injected was measured gravimetrically. After the required period, during which the patient remained at rest and fasting, 10 mls of venous blood was obtained, placed in a tube containing 10 units of heparin, centrifuged and the plasma drawn off. At the same time the patient was asked to empty the bladder and the urine passed over the period was collected. In one group of patients the stomach was continuously aspirated via a naso-gastric tube, and the aspirate collected over the same period.

Samples of plasma, gastric aspirate and urine were all counted to a total of at least 10,000 counts in a well type scintillation counter (thallium activated

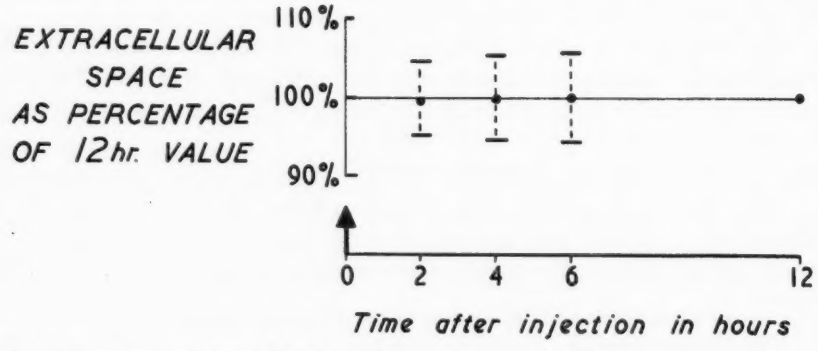

Fig. 1. Time required for equilibration after intravenous administration.

sodium iodide crystal). A sample of the injected solution diluted 1 part in 500 was also counted, from which the exact dose of isotope injected could be calculated. The chloride content of each sample obtained was determined by the Volhard titration method. The bromide space was then calculated as follows:—

1. Residual Dose = Administered Dose–(Loss in urine + Loss in aspirate).

2. $$\text{Bromide Space} = \frac{\text{Residual Dose (c/s)}}{\text{Plasma concentration (c/s/ml)} \times 1000} \text{ Litres.}$$

To convert this measured volume of distribution of ^{82}Br into the "extracellular fluid volume" it was multiplied by a factor of 0.9 to correct for Donnan equilibrium and for the amount of ^{82}Br entering the red blood cells (2); it is the extracellular fluid volume as derived from this calculation that has been used for the figures and tables in this text.

The rate of equilibration over 12 hours was studied in 6 patients admitted for investigation, or minor surgery only. The bromide space was measured in the manner described at 2, 4, 6, and 12 hours after injection, the urine being collected over each period and aliquots separately counted. In a further 5 similar patients the bromide space was measured once 12 hours after injection.

TABLE II

RELATIONSHIP OF EXTRACELLULAR FLUID VOLUME TO WEIGHT AND IDEAL BODY WEIGHT

Patient	*E.C.F.V. (Litres)*	*Body Weight (Kg)*	*Ideal Body Weight (Kg)*	*Patient*	*E.C.F.V. (Litres)*	*Body Weight (Kg)*	*Ideal Body Weight (Kg)*
1	10.19	35.7	51.2	20	15.4	58.8	67
2	16.13	58.2	68.4	21	12.2	58	65
3	18.55	56.8	83.8	22	14.2	49.4	63
4	19.9	69.1	72.9	23	14.3	67.8	68
5	17.0	57	61.2	24	13.7	58.2	62
6	15.3	54.2	67.5	25	23.5	106	91.1
7	15.3	53	64.8	26	14.2	49.5	63
8	10.75	38.1	53.9	27	12.9	63	53
9	17.6	63	81.1	28	9.2	35.5	52.1
14	13.45	55.8	59.8	29	18.0	67.1	74
15	11.6	49.8	53.9	32	15.0	59.5	70.7
16	15.3	53.2	63.5	35	14.8	63.4	65.7
18	12.6	39.8	59.3	38	15.9	69.3	59.8
19	16.1	51.2	68.4	39	13.7	57	55.1

In 17 other patients the bromide space was measured at between 12 and 15 hours after injection; in this group of patients, as well as the urine, the gastric aspirate was collected during the period of equilibration. These patients had either peptic ulceration or cholecystitis and the estimations were carried out over the night preceding operation. No cases with clinical or biochemical signs of an abnormality of the body fluids were included. The weight and height of each patient was recorded at the time of the test; the ideal body weight was obtained from the table relating this to height in Documenta Geigy Scientific Tables, 5th Edition, (J. R. Geigy S. A., Basle, 1956).

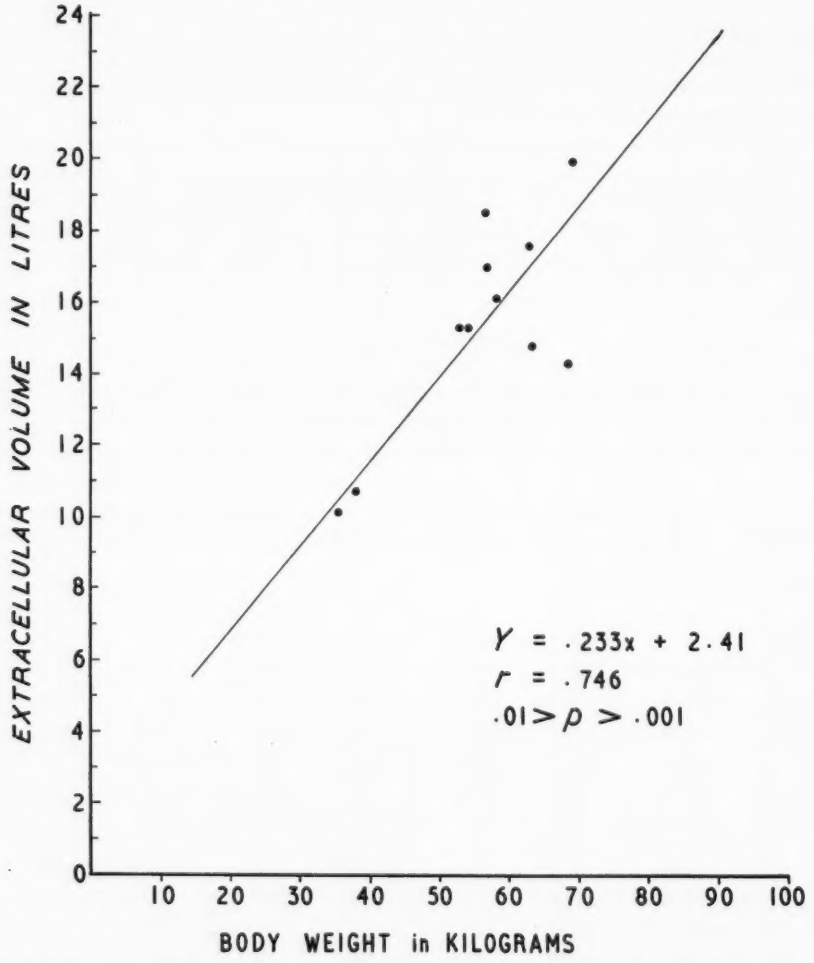

Fig. 2. Correlation between extracellular volume and body weight without allowance for ^{82}Br in gastric juice.

RESULTS

(a) *Time of equilibration.* (Table I Figure 1).

At 2 hours after injection the extracellular fluid volume averages 99.8 per cent of the 12 hour figure, the standard deviation being 2.35 per cent. There is no significant difference between the means at 2, 4, or 6 hours.

(b) *Relationship with body weight and ideal body weight.* (Table II. Figures 2 and 3)

The extracellular fluid volume measured at 12 hours, without gastric aspiration, was found to be closely related to both the body weight and the ideal body weight. It represented 27.5 per cent of the former (st. dev. =3.16) and 23.05 percent of the latter (st. dev. =2.51).

(c) *Concentration of isotope in the gastric aspirate and its effect on bromide space measurement.* (Tables II & III Figures 4, 5 & 6).

A selectively high concentration of ^{82}Br, when compared with the chloride content of the gastric aspirate, has been confirmed. The ratio of the observed ^{82}Br concentration to that which would be expected from the chloride concentration ranged from 11.4 − 2.4 : 1. The proportion of the administered dose of isotope

TABLE III

Patient	*Plasma Chloride in mEq/L*	*Percentage of Administered Dose/ml. (plasma)*	*Gastric Content Chloride in mEq/L*	*Percentage of Administered Dose/ml. (Gastric content)*	*Expected Percentage of Administered Dose/ml. (Gastric content)*	*(%) Total Dose Loss in Aspirate*	*Volume of Aspirate (ml.)*
14	96	—	115	—	—	10	—
15	98	.0048	136	.065	.0065	38.2	590
16	100	.0059	123	.0467	.00725	5	520
18	99	.0040	150	.0426	.0061	44	1030
19	109	.0042	150	.0230	.0058	24.8	1070
20	108	.00478	140	.0220	.0062	17.3	790
21	110	.00629	133	.0183	.0016	8.7	475
22	98	.0050	115	.0157	.0056	20	1270
24	98	.0060	116	.0170	.0071	8.3	470
25	110	.0036	131	.0140	.0043	5.7	410
26	101	.00415	150	.028	.00615	34.3	1200
27	108	.0045	125	.0312	.0052	35.2	1125
28	98	.0090	45	.0196	.00405	3.92	400
29	110	.0043	107	.030	.0042	13	425
32	104	.0053	123	.022	.00625	8.6	400
38	101	.0055	96	.0164	.0052	2.13	130
39	103	.00569	106	.031	.00585	6.4	200

present in the aspirate varied between 4 and 44 per cent (mean 20%) and the amount of isotope found in the aspirates varied with the volume collected during the period of equilibration. However, if allowance for this loss of injected isotope was made, the correlation between the extracellular fluid volume and the ideal body weight was found to be much closer than in the first group of patients in which the quantity of ^{82}Br in the gastric contents was unknown.

DISCUSSION

A single dose method of estimating the extracellular fluid volume with rapid equilibration has obvious advantages but the single dose techniques so far

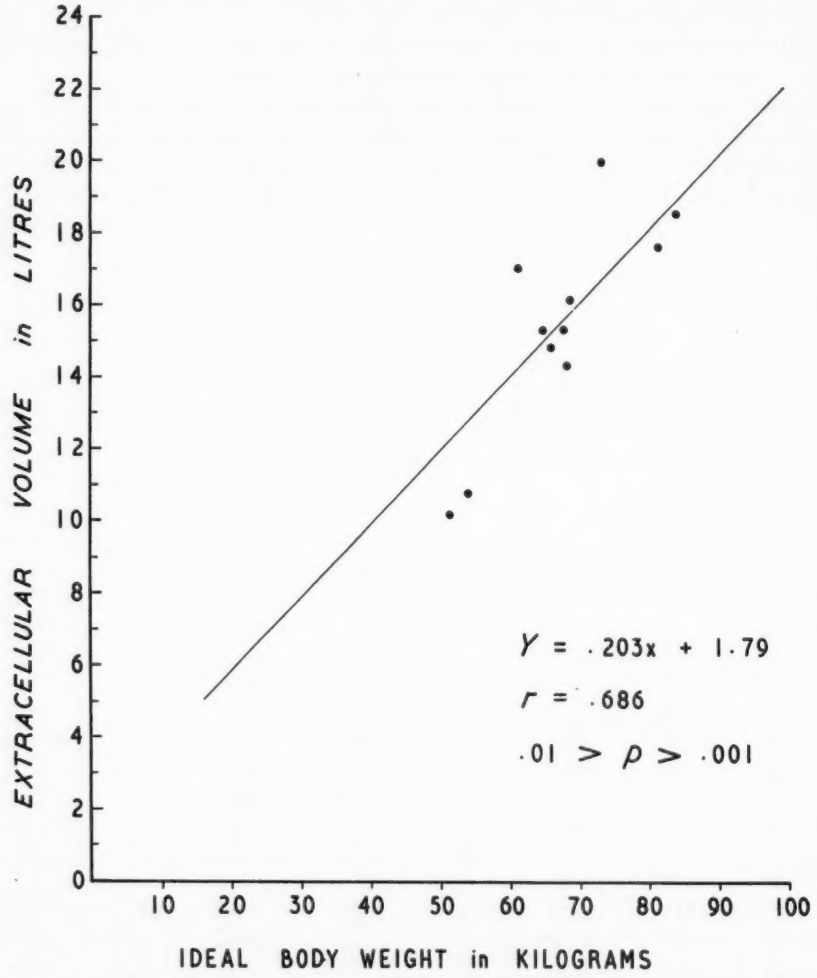

Fig. 3. Correlation between extracellular volume and ideal body weight without allowance for ^{82}Br in gastric juice.

used are all subject to serious inaccuracy. Thus thiocyanate (5) is selectively bound to the plasma proteins giving a false high result for the extracellular fluid volume (6). Investigation of the thiosulphate and radiosulphate methods of estimation have shown that the space measured is rapidly increasing with time and that a considerable degree of intracellular migration and metabolism occurs (7, 8, 9).

The measurement of the true "chloride space" with the isotopes of chloride itself is prevented by their unsuitable half-life. After administration of ^{82}Br orally it has been shown that 6 hours at least is needed for equilibration (10, 11) and that it may require as much as 12 to 18 hours (12). This study has shown that when given intravenously only 2 hours is needed for equilibration and this value stays stable for 12 hours; in some example we have found that it remains stable for more than 24 hours.

The high concentration of the isotope in gastric contents, previously reported after oral administration (13) has been confirmed in the present study after the intravenous administration of ^{82}Br. It is known that saliva also contains ^{82}Br in a concentration greater than that to be expected from the chloride concentration (2). In our series no attempt was made to separate the contributions individually made to the amount of isotope present in the gastric contents by the gastric and salivary secretions. It has been suggested that the whole of this intragastric pool is reabsorbed lower in the gastro-intestinal tract (14) and that

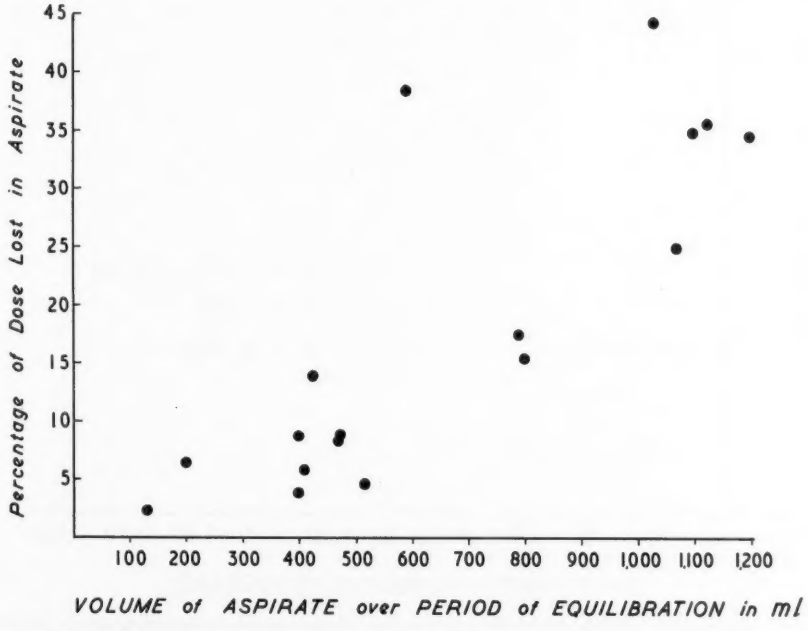

Fig. 4. Comparison of dose loss with volume of gastric aspirate during equilibration.

therefore this intra-gastric or "transcellular" ^{82}Br should be regarded as part of the total ^{82}Br space. The intra-gastric pool is, however, very variable in amount and if there is any degree of gastric obstruction its reabsorption is hampered. This would cause a wide variation in the value calculated for the bromide space because of the very large range of dose loss into the stomach that we have found.

It has been shown that the extracellular fluid volume is closely related to the ideal body weight (15) and for that reason this particular parameter has

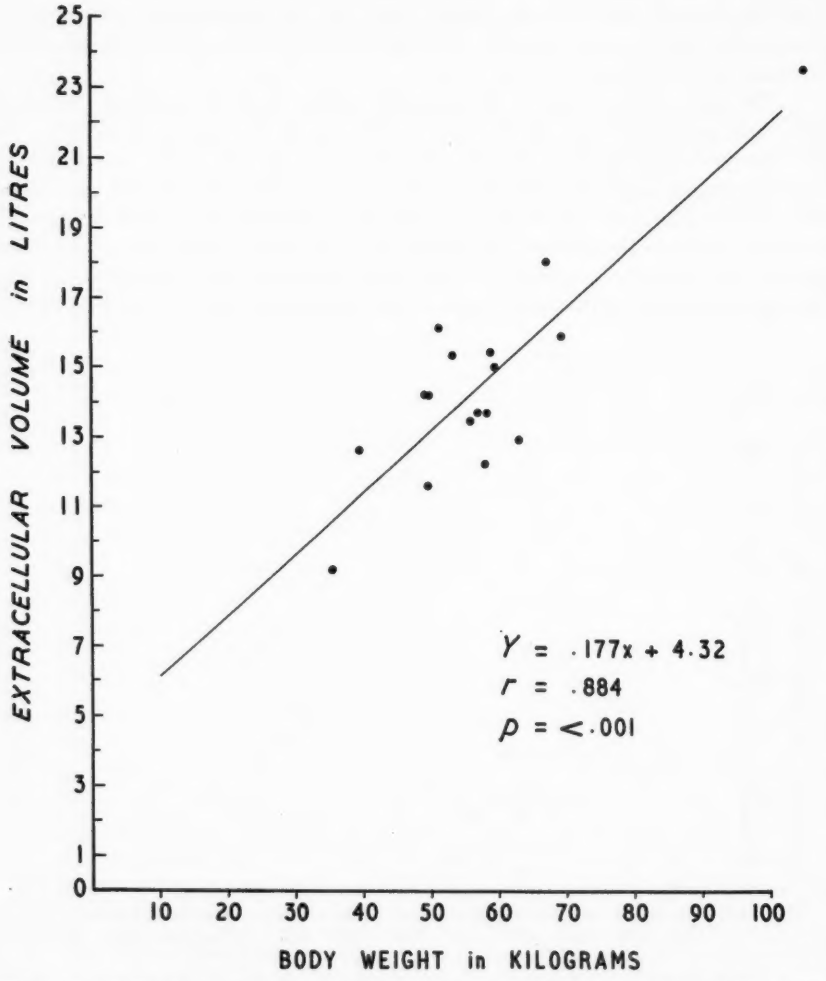

Fig. 5. Correlation between extracellular volume and body weight allowing for gastric loss of isotope.

been used for comparison with the figures determined for the extracellular volume in this study. In the first series of patients, the extracellular fluid volume represented 23.05 per cent of the ideal body weight; in the second series of patients where the quantity lost in the gastric aspirate was kown, the extracellular fluid volume represented 22.6 per cent of the ideal body weight, and the correlation between the two was much closer. The extracellular fluid volume in animals was 21.8 per cent of the body weight in one series of experiments (16).

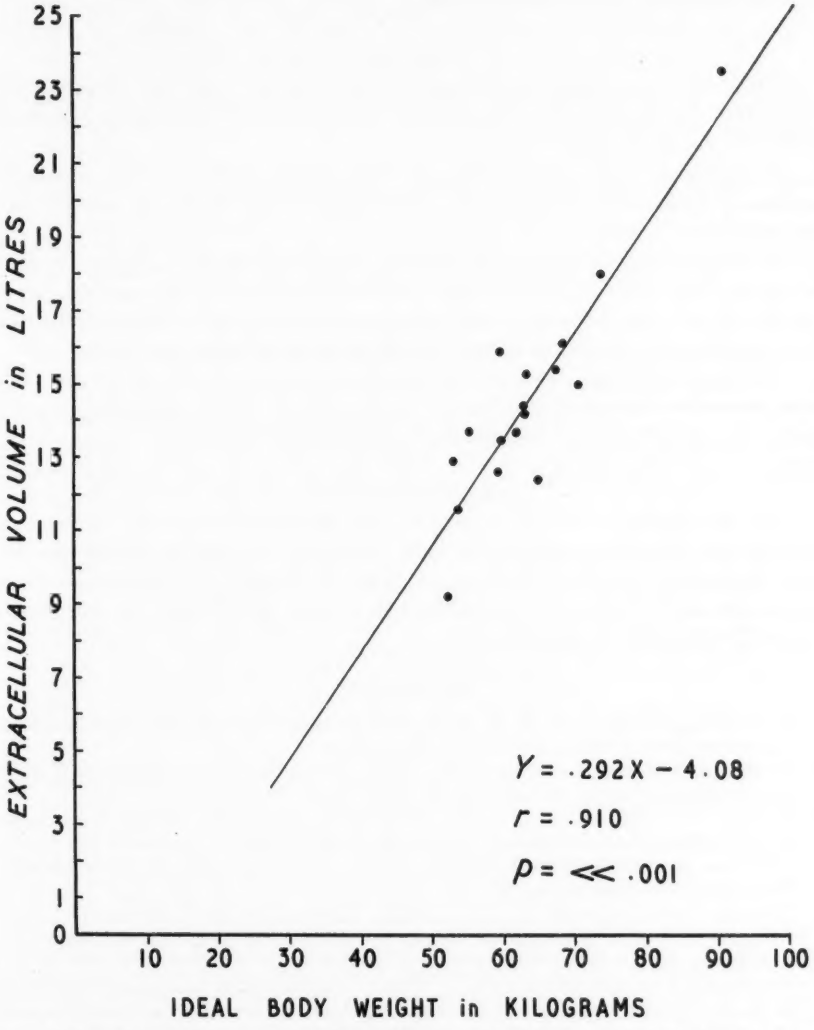

Fig. 6. Correlation between extracellular volume and ideal body weight allowing for gastric loss of isotope.

This figure is so close to the mean value found in our patients (22.6%) that it suggests that the intravenous use of ^{82}Br is an accurate method for determining the extracellular fluid volume provided that the main source of error, *i.e.* the pooling of isotope in the stomach contents is excluded.

The short equilibration period of this method means that it can be applied in patients with body fluid depletion requiring replacement therapy shortly after their admission to hospital. We have employed it clinically in such patients with pyloric stenosis where the gastric losses are large, and the method remains applicable in such circumstances.

SUMMARY

After the intravenous administration of ^{82}Br in man the isotope was completely distributed after 2 hours and the volume of distribution remained stable for at least 12 hours.

A selectively high concentration of ^{82}Br in the gastric contents has been confirmed. An average of 20 per cent of the administered dose was secreted into the stomach in 12 hours.

If allowance was made for this dose loss into the stomach, in addition to that lost in the urine, the extracellular fluid volume determined by this method represented 22.6 per cent of the ideal body weight and the correlation between the two is closer than when the loss of isotope into the stomach is unknown.

It is suggested that the intravenous administration of ^{82}Br is a rapid and accurate method for measuring the extracellular fluid volume, provided that the gastric loss of isotope over the period of equilibration is known.

ACKNOWLEDGEMENTS

We are grateful to Mr. D. H. Patey & Mr. L. P. LeQuesne for allowing us to investigate their patients and for their advice; to the patients themselves for their cooperation; to Dr. E. Williams & Miss M. Davies for their technical assistance; to Miss Hewland, our medical artist and Mr. Turney, of the Photographic Department, for the figures.

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DR. SHIELDS WARREN NAMED TO RECEIVE USAEC CITATION

Glenn T. Seaborg, Chairman of the Atomic Energy Commission, today announced that Dr. Shields Warren, for many years one of this country's leading authorities on atomic radiation, has been named to receive the Atomic Energy Commission Citation.

Dr. Warren is Scientific Director of the New England Deaconess Hospital's Cancer Research Institute, Boston, and professor of pathology at Harvard University. He will receive the AEC citation because of his outstanding service as U. S. Representative to the United Nations Scientific Committee on the Effects of Atomic Radiation.

CITATION TO DR. SHIELDS WARREN

> Distinguished Pathologist and Scientist-Statesman for his meritorious contribution to the United States Nuclear Energy Program as the U. S. Representative to the United Nations Scientific Committee on the Effects of Atomic Radiation, 1955-1963. His prior service to the U. S. Atomic Energy Commission as Director, Division of Biology and Medicine, 1947-1952 and as member, Advisory Committee for Biology and Medicine, 1952-1958 is a record of outstanding accomplishments. His scientific knowledge, leadership, and dedicated service have contributed immeasurably to the U. S. and the world scientific community.

The Atomic Energy Commission Citation was established for presentation to persons not in the employ of the Commission who have made meritorious contributions to, or have been outstanding in, the nuclear energy program. Private individuals and employees of AEC contractors, of other U. S. government departments or agencies, including the military, and of industrial, educational and research establishments are eligible to receive the award.

He served as first assistant in pathology at the Boston City Hospital until 1925 when he returned to Harvard as instructor in pathology.

After serving five years as the first Director of the AEC's Division of Biology and Medicine, he resigned in 1952. For the next six years he was a member of the AEC Advisory Committee for Biology and Medicine. At the present time he is conducting research on radiation effects at New England Deaconess Hospital under an AEC contract.

Dr. Warren was chief of the naval medical field team that investigated the effects of the bombing of Hiroshima and Nagasaki. He had charge of pathological studies conducted on the animals exposed to radiation in two series of bomb tests at Bikini, and was a member of the Committee on Pathology and the Advisory Committee on the Atomic Bomb Casualty Commission of the National Research Council. He was special consultant to the chief of the Navy Bureau of Medicine and holds the rank of Captain (retired), USNR MC. During the eight years he was U. S. Representative to the United Nations Scientific Committee on the Effects of Atomic Radiation he made valuable scientific contributions and also provided excellent leadership in the interest of his country.

Dr. Warren is a member of the Society of Nuclear Medicine and a Consulting Editor of the Journal of Nuclear Medicine in addition to holding membership in many scientific organizations.

JOURNAL OF NUCLEAR MEDICINE 4:480-484, 1963

Isotopic Labeling of the Rat Parathyroid as Demonstrated by Autoradiography.[1]

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Boston

INTRODUCTION

The present experiments were initiated to attempt localization of the parathyroid glands by isotopic means and to develop a technique for the *in-vivo* labeling of parathyroid hormone for further analysis of its metabolism. Specific emphasis was placed on a study of selective localization in the parathyroid of isotopically labeled amino acids in an experimental model as a potentially useful clinical tool.

A primary function of the parathyroid gland is the formation of polypeptide or small protein hormones which have been analyzed chemically by Rasmussen. (1) It has been shown that administered amino acids go rapidly into protein anabolism. In attempting to label the parathyroid gland with isotopic amino acids the main theoretical problems were: (1) The differential anabolism in the immediate area under analysis and, (2) The relative accretion of the specific amino acid.

METHOD

The first practical problem to be faced was the development of an experimental model in which the parathyroid activity was the most pronounced anabolic activity in the region under analysis. The rat was chosen as the experimental animal because it is relatively inexpensive and because anatomically it has two parathyroid glands which are reliably located in the region of the superior pole of the thyroid glands. In these experiments 200 gm white female Sprague-Dawley strain rats were used. Considerable difficulty was encountered initially in obtaining consistently good histologic sections of the parathyroid glands because of their minute size. By doing serial neck sections in paraffin block preparations, it is now possible to identify the parathyroid glands in unstained microscopic sections with the use of the light microscope.

For use in autoradiography, it is necessary to have unstained sections with a minimum of biochemical alteration of parathyroid hormone. There has been some concern over the effect of tissue preparation on the parathyroid hormone, in that biochemical reaction may significantly alter the hormone and result in

[1]This project has received the 1963 John J. Larkin jr Memorial Award for research in Basic Medical Science.

[2]Harvard Medical School Department of Radiology at the Peter Bent Brigham Hospital.

lack of ability to demonstrate radioactive incorporation. It is known that formalin decreases the physiologic activity of the hormone and that parathyroid hormone is soluble in alcohol. Therefore, the routine preparation of formalin fix, alcohol, xylol, and paraffin block was considered too risky for autoradiographic preparation in this instance. We have therefore fixed in acetone, with benzene dehydration, and paraffin histologic method. Although this has been adequate to demonstrate the gland, intracellular detail is obscured by this fixation. Present attempts are directed toward a method of formalin fixation with acetone dehydration.

Davis and Enders (2) have shown rather marked parathyroid hyperplasia and hypertrophy 48 hours after bilateral nephrectomy in rats. It was originally intended to use this technique in an experimental model to effect a relative increase in parathyroid anabolism. However it was found that after bilateral nephrectomy the 48 hour survival was not sufficiently dependable to utilize this method to stimulate the parathyroid glands. The majority of rats died in about 24-36 hours. Although there were some changes in parathyroid histology, the severe alteration of total body metabolism with the resultant lack of tolerance to subsequent anesthesia for isotope injection demanded the development of another method of parathyroid stimulation.

Alternatively, a group of rats was placed on a low calcium diet obtained from Nutritional Biochemical Co. This consisted of purified casein 24 per cent, sucrose 68 per cent, vegetable oil 5 per cent, calcium free salt mixture 3 per cent, and vitamins. After eleven days of this diet an animal was sacrificed and the neck organs were examined. There was observed a histological suggestion of increased parathyroid activity manifested by parathyroid hyperplasia and hypertrophy. In view of the fact that the animals appeared to tolerate this diet well and survival was no problem, it was deemed advisable to continue this method in the experimental model.

One of the major concerns in attempting to develop a technique for subsequent clinical localization of hyperactive parathyroid glands has been the relative protein anabolism in the area under analysis. Obviously the thyroid, because of its bulk, would be the most probable source of extraneous radioactive emission. In view of this the suppression of thyroid anabolism was considered essential. Originally some thought was given to the use of thyrotoxic drugs. Rather, it was decided that the injection of thyroxine would be a safer, more physiologic, and more effective means of suppressing thyrogloubin metabolism. Therefore rats were injected with 20 micrograms of L-thyroxine sodium pentahydrate subcutaneously every other day for a total of six injections. This resulted in a rather striking histologic change in the thyroid gland, manifested by fatty infiltration and fibrosis. The animals tolerated this dosage well and there was no evidence of hyperactivity. In an attempt to confirm physiologic thyroid suppression, four rats (2 control and 2 thyroxine treated) were given I^{131} intraperitoneally. The thyroid glands were excised at 48 hours and the radioactivity was counted. The controls had an uptake of 9 per cent and 12 per cent respectively. The test rats had an uptake of 0.1 per cent and 0.005 per cent. In view of this it was decided to include this method of thyroid anabolism suppression in the experimental model.

The other main theoretical problem was the selection of a labeled amino

acid which would have a relatively greater accretion in the parathyroid gland than in surrounding structures. Isolated parathyroid polypeptides have been shown by Rasmussen (1) to be relatively high in glutamic acid (about 14%) while Bersin (3) has shown thyrogloubin to be specifically low in this amino acid. No physiologic radioactive glutamic acid compounds with a gamma emission amenable to external counting are now available. It was, therefore, decided to use a sulfur containing amino acid. Some encouragement was derived from the literature on histone anabolism that tryptophane had the highest specific activity of incorporated amino acids, which was surprising in view of the fact that histones are said to contain only traces of tryptophane.

Based on the work of Hansson (4), who demonstrated the rapid accumulation of S^{35} amino acids in pancreatic tissue and enzymes, Bender and Blau (5) have been able to label the pancreas clinically with Se^{75} selenomethionine. In this initial study it was felt that autoradiography would provide more definite assessment of parathyroid activity than external counting. Tritiated methionine was selected over S^{35} methionine because of a more reliable specific activity and an energy emission more favorable to quality autoradiographs.

Bender and Blau (5) have shown the best results with external scanning over the pancreas in patients who have been fed a high protein diet. Theoreti-

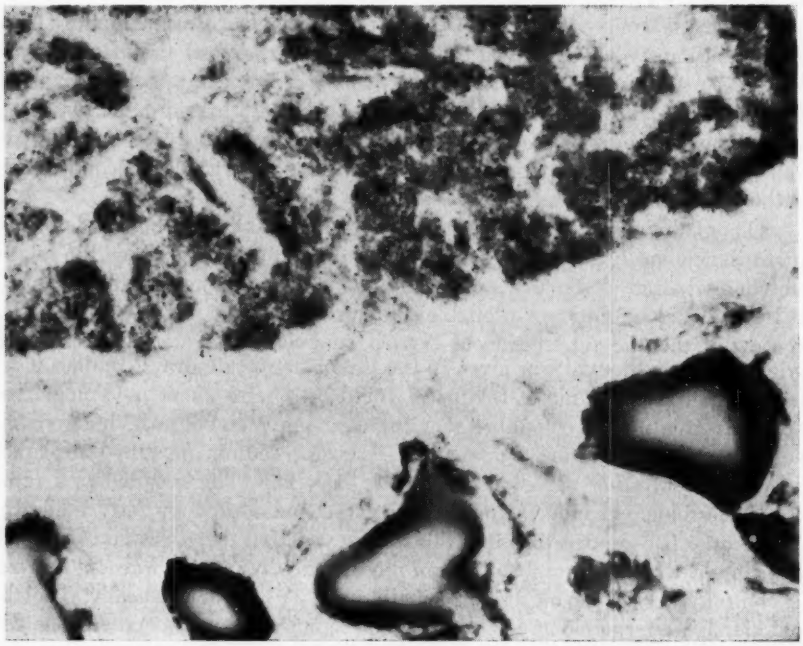

Fig. 1. Photomicrograph ×600 of a 10 micron section of rat parathyroid, Cason stain. Section for autoradiograph taken 10 minutes after injection of 1000 microcuries of tritiated methionine into inferior vena cava. Note selective localization of radioactivity to parathyroid tissue in upper half of photograph.

cally, pre-feeding with a high protein diet should "pack" the protein stores so that a relatively higher concentration of the injected amino acid would go to the area of greatest protein anabolism. Therefore, the low calcium diet in the experimental model was modified by the addition of 2 lbs. pure calcium free casein and 500 mg of methionine to 2 lbs. of the original low calcium diet. The new diet consisted of casein 62 per cent, sucrose 34 per cent, vegetable oil 2.5 per cent and calcium free salt 1.5 per cent plus vitamins and 0.5 gms of methionine. Parathyroid glands were examined after eleven days of the low calcium diet followed by seven days of low calcium, high protein and high methionine diet. These too showed evidence of increased activity, manifested by hyperplasia and hypertrophy.

Following these developmental experiments a trial run with H^3 methionine was initiated. A group of rats were prepared by eleven days of low calcium diet followed by seven days of the low calcium, high protein, and high methionine diet for a total of eighteen days of a controlled diet. They each received 20 micrograms of L-thyroxine sodium pentahydrate subcutaneously every other day for a total of six injections. Tritium labeled methionine in dosages ranging from 250 microcuries to 1000 microcuries were injected into the inferior vena cava. The animals were sacrificed at 5, 10, and 30 minutes following the injection, and the neck organs were removed and fixed in acetone, for benzene, paraffin histologic preparation. The liver, kidney, spleen, pancreas, and salivary glands were also biopsied for eventual autoradiography in an attempt to evaluate the distribution of the labeled methionine. The neck organs were serially sectioned and the parathyroids were located. The unstained slides were dipped into Kodak NTB2 emulsion and the autoradiographs were developed at 10, 20, and 30 days, then subsequently stained with a cason stain.

RESULTS

The parathyroid glands are well visualized and there is a rather marked selective labeling over them in all animals. The labeling is heaviest in the 1000 microcurie treated animal; however, there are no other 1000 microcurie treated animals. In comparing the animals which received 250 microcuries at 5, 10, and 30 minutes, the labeling is heaviest at 30 minutes. It was anticipated that the evaluation of intracellular detail would be limited by the acetone fixation. Further experiments using formalin fixation but using benzene dehydration to bypass the alcohol phase are underway. With this method the histologic detail should be improved.

DISCUSSION

The ability to selectively label the parathyroid gland with a high energy gamma emitting radioisotope would be exceedingly helpful in localizing a hyperactive gland either by external scanning or surgical probe counting. Thus far, an apparently reliable experimental model which manifests a relative selective uptake by the parathyroid gland of radioactive methionine has been developed. Since the metabolic pathways of the labeling sequences have not been defined, it is premature to assume that comparable localization will be obtained with seleno-

methionine. In this regard, however, it should be pointed out that the exact chemical mechanism is not critical provided the localization of radioactivity to the gland reflects the synthetic flux of parathormone.

The lack of amino acid uptake by the thyroid gland following the administration of thyroxine suggests that an important mechanism of Thyroid stimulating hormone upon the thyroid gland is related to the stimulation of protein anabolism. Various experiments to further delineate this mechanism are in progress.

The fact that in this experimental model the parathyroid accretes a significant amount of methionine is interesting because of the relatively low concentration of methionine in parathyroid hormone. In view of this further work on the incorporation of glutamic acid and lysine into the parathyroid gland is being planned, as a preliminary to a study of the physiologic activity of the labeled incorporated compound.

SUMMARY

The rat parathyroid has been isotopically labeled with relative selectivity using tritiated methionine as demonstrated by autoradiographic techniques. The parathyroid function was stimulated by a low calcium diet. Thyroid anabolism, which is the most probable source of extraneous radioactive emission, was effectively suppressed with thyroxine. This initial breakthrough in selective isotopic labeling of the parathyroid glands has many ramifications some of which are discussed.

ACKNOWLEDGEMENTS

The author acknowledges the assistance of the following members of various Harvard Medical School and Peter Bent Brigham Hospital Departments: Doctors James B. Dealy, Jr., S. James Adelstein, Daniel Bernstein, Herbert Selenkow, Arthur Like, Donald Feldman, Jean P. Ravel and Elizabeth Hay. In addition I express appreciation for the technical assistance of Richard Rebell.

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JOURNAL OF NUCLEAR MEDICINE 4:485-486, 1963

PRELIMINARY PROGRESS NOTE[1]

Extrapolation of Precordial Counting Curves[2]

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INTRODUCTION

The use of gamma emitters and precordial counting for determination of cardiac output has gained popularity because it precludes the need for intra-arterial sampling and because the calculations can be relatively quickly accomplished. The time required for the procedure is minimized by direct inscription of the precordial indicator dilution curve on rectilinear chart paper and determination of the area under the curve by tracing its perimeter with a polar planimeter. For use in the formula for cardiac output, this figure must include only the area under the primary circulation curve. Therefore the inscribed downslope must be extrapolated from the start of recirculation down to pre-injection baseline (1-3).

In general, the downslope of primary circulation curves follows rather closely an exponential course (4). This is used as a guiding principle in extrapolation of the inscribed curves. At present this extrapolation is accomplished with accuracy in most laboratories by replotting of the inscribed curved downslope on semi-log paper where it assumes a straight line. The extrapolation is easily carried out by extension of the line but must be replotted on the original rectilinear chart for measurement of total curve area. This procedure is tedious and adds considerable time to the whole cardiac output method. Computers designed to perform this calculation have recently been announced but these are expensive and may have limitations in accuracy in certain types of curves.

Direct extrapolation of the original rectilinear curve by visual inspection and drawing along a "properly placed" French curve, while saving time, is not considered to furnish the accuracy or consistency commensurate with the other parts of the technic.

This preliminary note is meant to publicize an inexpensive device which the authors have found useful for the accurate, reliable and rapid extrapolation of directly recorded precordial curves.

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[1]Preliminary Progress Note, see page 452.

[2]From the Departments of Internal Medicine and Biometrics, School of Aerospace Medicine, Brooks Air Force Base, San Antonio, Texas.

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METHOD

A set of exponential curves, embracing a variety of downslopes likely to be encountered in human cardiac output curves, was designed for use as an underlay beneath rectilinear charts on which are inscribed precordial counting curves. Each curve of the set represents log y = kt where the vertical scale y is arbitrary but common to the entire set. The origin of the horizontal time scale (t) is moved over slightly for each curve in order to avoid overlap. The constant k, describing the shape or downslope or time constant of a given curve, is changed from curve to curve by small increments to provide the desired variety. The set can be used with any width chart so long as the downslope falls within the range of the set. Although a set of exponential curves may be constructed by plotting for each curve many points from a log table, the set used by the authors was produced by an analog computer solution of $\dot{y} = ky$ on an X-Y plotter, setting k for each curve by a simple turn of a potentiometer. Once drawn, mounted on a firm backing, and protected with a transparent cover, such a device will be useful for many years.

With the pre-injection baseline of each inscribed curve superimposed on the common base level of the set of exponential curves, and by sliding the upper record along the underlay, it is easy to quickly select the exponential curve which matches the inscribed part of the downslope. A deviation of the latter is then easily identifiable and represents the start of obvious recirculation. Correct exponential extrapolation past this point can be readily accomplished by tracing with a pencil the rest of the exponential curve as seen through the rectilinear chart paper.

RESULTS

Calculation of approximately 500 precordial counting curves over a two year period has indicated the usefulness of this labor-saving device. Results were compared with semi-log plotting and extrapolation in 25 consecutive cardiac output determinations with patients at rest or performing exercise (range 2.6 − 7.3 L/min/M^2). It was found that the new device matched semi-log plotting in practice as well as in theory. However, it is considerably less tedious and time-consuming. In this way, one can avoid the temptation to save time by extrapolation based on visual inspection and drawing along a part of a French curve.

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INDEX

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VOL. 4, 1963

CONTENTS

VOLUME 4 JANUARY, 1963 NO. 1

W. Paul, Ph.D., and E. H. Botterell, M.D. An Appraisal of As-^{74} for Localization of Brain Tumours 1

Sydney Kofman, M.D., Howard H. Sky-Peck, Ph.D., Yvian Thibaudeau, M.D., Robert D. Ray, M.D., and Samuel G. Taylor, III, M.D. The Use of Strontium-85 in the Evaluation of Bone Metastases. A Preliminary Report 9

Francis T. Oda, M.D., William D. Gibbs, B.S., and Gould A. Andrews, M.D. Distribution of Radioisotopes in Tumors of the Rat Liver 18

Benjamin Calesnick, M.D., and Arthur Wase, Ph.D. Absorption and Excretion of Radioactive Hg^{203} Mercaptomerin Sodium in Humans 29

P. Czerniak, M.D., E. Lubin, M.D., M. Djaldetti, M.D., and A de Vries, M.D. Scintillographic Follow-up of Amoebic Abscesses and Hydatid Cysts of the Liver 35

Felix J. Pircher, M.D., Audrey V. Wegst, A.S., M.S., and Vernon N. Dodson, M.D. In Vitro Analysis of the Radioisotope Renogram Test 45

R. F. Doering, W. D. Tucker, and L. G. Stang, Jr. A Simple Device for Milking High-Purity Yttrium^{90} from Strontium^{90} 54

Fabian, A. O., Udekwu, M.D., Donald D. Kozoll, M.D., and Karl A. Meyer, M.D. Determination of Total Body Water with Tritium Oxide ($H_2{}^3O$) 60

I. Meschan, M.D., Tom Hosick, B.S., Herman Schmid, M.D., and F. C. Watts, B.S. Variability in Renal Clearance Rate Studies Using Fresh $OI^{131}HA$ Purified Product and Stored Product 70

Maurice J. Small, M.D., Wade N. Miller, M.D., George C. Leiner, M.D., Herbert D. Strauss, A.B., and Sol Abramowitz, B.S. The I^{125} Radiopulmogram 78

VOLUME 4 MARCH, 1963 NO. 2

THOMAS P. HAYNIE, AND WILLIAM H. BEIERWALTES, M.D. Hematologic Changes Observed Following I^{131} Therapy for Thyroid Carcinoma 85

RUTH C. STEINKAMP, M.D., JOHN H. LAWRENCE, M.D., AND JAMES L. BORN, M.D. Long Term Experiences with the Use of P^{32} in the Treatment of Chronic Lymphocytic Leukemia 92

ARTHUR C. BEALL, JR., M.D. AND PHILIP C. JOHNSON, M.D. Use of the Radioisotope Renogram in the Differential Diagnosis of Renal Insufficiency Following Vascular Surgery 106

FELIX J. PIRCHER, M.D., EDWARD A. CARR, JR., M.D., AND MARY ELLEN PATNO, PH.D. Evaluation of Quantitative Aspects of the Radioisotope Renogram 117

L. VAN MIDDLESWORTH, M.D., PH.D., JO AUBREY TURNER, B.S., AND ALYS LIPSCOMB, M.D. Liver Function Related to Thyroxine Metabolism 132

JOSEPH L. RABINOWITZ, PH.D., BERNARD SHAPIRO, M.D., AND PHILIP JOHNSON, M.D. "Sephadex Chromatographic" Test in the Evaluation of Thyroid Function 139

DAVID L. JOFTES, PH.D. Radioautography, Principles and Procedures 143

LEOPOLDO J. ANGHILERI, PH.D. A Chromatographic Study of the Stability of Iodine-131 Labeled Sodium o-Iodohippurate 155

H. W. WEIGEL, M.D., J. PARSONS, M.D., H. ELRICK, M.D., C. J. HLAD, JR., M.S., E. MILLER, M.S. The Excretion of Na^{22} in Sweat 159

R. T. MORRISON, M.D., J. A. BIRKBECK, M.B., CH.B., T. C. EVANS, PH.D., J. I. ROUTH, PH.D. Radioiodine Uptake Studies in Newborn Infants 162

VOLUME 4 MAY, 1963 NO. 3

Program—Tenth Annual Meeting 169

Abstracts—Tenth Annual Meeting 181

Technical Exhibitors 218

Scientific Exhibitors 220

President's Annual Report 223

Officers, Executive Committee and Board of Trustees 225

Professor Emilio Segré—Fourth Annual Nuclear Pioneer Lecture in honor of Professor Enrico Fermi 227

W. H. Oldendorf, M.D. and M. Kitano, M.D. Selenomethionine Reappearance in Blood Following Intravenous Injection 231

A. S. McFee, M.D., N. B. Ackerman, M.D., and M. K. Loken, Ph.D., M.D. The Prevention of Hepatic Metastasis by the Use of a Colloidal Suspension of Radioactive Chromic Phosphate ($CrP^{32}O_4$) 234

F. H. Foeckler, Jr., Sc.D., N. M. Bering, M.T. (ASCP), J. Siragusa, M.T., (ASCP), and O. B. Hunter, Jr., M.D. Comparative Thyroid-Function Studies with the Resin T-3 Test. 239

M. A. Razzak, M.D. The Use of a Modified Radioactive Test for Evaluating The Peripheral Circulation. 244

VOLUME 4 **JULY, 1963** **NO. 4**

Raymond G. Rose, M.D., James E. Hartfield, M.D., Mavis P. Kelsey, M.D., and Eleanor J. MacDonald, A.B. The Association of Thyroid Cancer and Prior Irradiation in Infancy and Childhood. 249

Ismael Mena, M.D., Pablo Thomsen, M.D., and Leslie R. Bennett, M.D. Determination of Coronary Blood Flow Index by External Scintillation Detection. 259

Paul V. Harper, M.D., Warren D. Siemens, Katherine A. Lathrop, M.S., and Harold Endlich, M.D. Production and Use of Iodine-125. 277

Murray L. Janower, M.D. A Query Into the Use of Tracer Doses of I^{-131}. 290

Milton G. Crane, M.D., John E. Holloway, M.D., Ralph Adams, B.A., and Ivor C. Woodward, M.A. The Relative Mean Transit Times of Red Cells and Plasma in the Portal Circulation of the Dog. 296

Barney T. Watson, M.A. Computers in Activation Analysis 306

Franklin T. Brayer, M.D. Influence of Plasma from a Variety of Stressed Animals on I^{131} Uptake in Chick Embryos. 312

J. U. Schlegel, M.D., R. M. O'Dell, Ph.D., and J. L. Izenstark, M.D. Importance of Stop Flow to Kidney Scans. 320

Hal O. Anger, B.S. and Alexander Gottschalf, M.D. Localization of Brain Tumors with the Positron Scintillation Camera 326

VOLUME 4 SEPTEMBER, 1963 NO. 5

D. Bruce Sodee, Major, MC A New Scanning Isotope, Mercury^{197} A Preliminary Report. 335

Hyo H. Byun, M.D., Gisela Albrecht, M.D., George W. Holmes, M.D. and Robert Landauer, Ph.D. Pulmonary Function Test Using Krypton-85. 345

Walter DiGiulio, M.D., Paul Weinhold, Ph.D., and George E. Thoma, Jr., M.D. The Thyroxin-Protein Dissociation Index, A Modified T_3 Resin Uptake Procedure. 359

Gerald J. Hine, Ph.D., Melvin H. Farmelant, M.D., John A. Cardarelli, M.A. and Belton A. Burrows, M.D. Four Channel Magnetic Tape Recording and Digital Analysis of Radio-Hippuran Renal Function Tests in Normal Subjects 371

Cleamond D. Eskelson, M.D., Arthur L. Dunn, Ph.D., Richard E. Ogborn, M.D. and John F. McLeay, M.D. Distribution of Some Radioiodinated Tetracyclines in Animals. 382

P. C. Johnson, M.D. and T. R. Redding, B.S. Glucose-1-C-14 Oxidation by Blood: A Potential Test for Tissue Effects of Thyrotoxicosis. 393

William H. Oldendorf, M.D. Supplementing the Rate Meter by Adding an Efficient Low-Pass Filter. 399

G. V. Taplin, M.D., E. K. Dore, M.D., and D. E. Johnson, M.D. The Quantitative Radiorenogram for Total and Differential Renal Blood Flow Measurements 404

Leopoldo J. Anghileri, Ph.D. A Study of the Stability of Neohydrin (3-Acetoxymercuri-2-Methoxypropylurea) Labeled with Mercury-203. 410

Current Abstracts in Nuclear Medicine 413

President's Letter 415

MILLARD N. CROLL, M.D., LARRY H. SHUMAN, M.D., LEONARD STANTON, M.S. AND CASIMIR CZARNECKI, M.D. Radioisotope Placentograph: A Bedside Procedure. 417

H. HOROWITZ, M.D., J. G. KEREIAKES, PH.D., E. L. SAENGER, M.D. AND THEODORE SELKIRK, JR., M.D. Liquid Scintillation Counting of I^{131} in a Clinical Laboratory. 426

GERALD J. HINE, M.D. Color-Coded Digital Print-Out for Radioisotope Scanning. 439

ROBERT C. MEADE, M.S., M.D. AND DONALD A. FRANKLIN, M.D. Results of a Standardized Hippuran Renogram. 446

JOHN E. KEARNS, M.D. AND WILLIAM HUTSON, M.D. Tagged Isomers and Analogues of Thyroxine (Their Transmission Across the Human Placenta and Other Studies). 453

F. S. EBERTS, JR., AND E. P. MARKOVICH. A Digital-Computer Method for Rapid Radioactivity Calculations. 462

C. T. HOWE AND R. P. EKINS. The Bromide Space After the Intravenous Administration of ^{82}Br. 469

E. JAMES POTCHEN, M.D. Isotopic Labeling of the Rat Parathyroid as Demonstrated by Autoradiography. 480

RALPH J. GORTEN, M.D., AND HARRY M. HUGHES, PH.D. Extrapolation of Precordial Counting Curves (Preliminary Progress Note) 485

Index 487

President's Letter vii

Editorial Page ix

First Call for Papers xiii

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I *Samuel N. Turiel, Managing Editor* of the *Journal of Nuclear Medicine*, certify that the statements made above are correct and complete.

AUTHORS INDEX

*Indicates abstracts of papers presented at 10th Annual Meeting of Society of Nuclear Medicine.
‡Indicates abstracts from *Current Literature*.

A

Abramowitz, S., 78
Ackerman, N. B., 234, 332‡
Adams, R., 296
Albrecht, G., 345
Allen, T. D., 185*
Alpern, H., 201*
Amato, C. G., 204,* 204*
Anderson, I. O., 83‡
Andrews, G. A., 18
Anger, H. O., 326
Anghileri, L. J., 155, 410
Ariel, I. M., 186*

B

Bajun, H. H., 345
Banerjee, R. M., 83‡
Banks, W. C., 184*
Barbour, B. H., 332‡
Bartter, F. C., 332‡
Batsakis, J. G., 167‡
Bauer, F. K., 207*
Beall, A. C. Jr., 106
Beierwaltes, W. H., 85
Bell, P. B., 183*
Bell, R. L., 214*
Bender, M. A., 186*, 193*
Bennett, L. R., 259
Berg, M., 208*
Bering, N. M., 239
Berliner, W. P., 202*
Birkbeck, J. A., 162
Blahd, W. H., 183*, 198*
Blau, M., 186*, 193*
Blum, J. A., 332‡
Blum, R., 201*
Bonte, F. J., 185*
Born, J. L., 92
Botterell, E. H., 1
Bourne, H. R. Jr., 213*
Bow, T. M., 201*
Brault, A., 215*
Brayer, E. T., 312
Brown, D. W., 197*
Bruneau, R., 210*
Burkle, J., 195*
Burnett, G. R., 167‡
Burrows, B. A., 371
Byun, H. H., 345

C

Caine, W. P. Jr., 190*
Calesnick, B., 29
Carbone, J. V., 83‡
Cardarelli, J. A., 371
Carlton, J. E., 208*
Carr, E. A. Jr., 117, 200*
Cassen, B., 181*
Chaitchik, S., 191*
Charkes, N. D., 194*
Chobanian, A. V., 413‡
Christie, J. H., 189*
Clapham, W. F., 332‡
Coberly, J. A., 199*
Cohen, D. W., 216*
Cope, C. B., 182*
Corday, E., 201*
Corey, K., 194*
Corrigan, K. E., 184*
Cousineau, L., 188*
Crane, M. G., 296
Croll, M. N., 417
Czarnecki, C , 417
Czerniak, P., 35, 191*, 197*

D

De Vries, A., 35
Dealy, J. B., 203*
Decker, C. F., 217*
Dettman, P., 195*
Dewey, W. C., 206*
Digiulio, W., 215*, 359
Dingwall, D., 331‡
Djaldetti, A., 35
Dodson, V. N., 45
Doering, R. F., 54
Dollery, C. T., 82‡
Dore, E. K., 193*, 209*, 404
Dratz, A. F., 199*
Dunn, A. L., 382

E

Eberts, F. S. Jr., 462
Edwards, L. R., 167‡
Eichorn, R. D., 212*
Ekins, R. P., 469
Elrick, H., 159
Endlich, H., 277
Endow, J. S., 198*
Engelberg, W., 333‡
Eskelson, C. D., 382
Evans, T. C., 162

F

Fairchild, R. G., 205*
Faloon, W. W., 167‡
Farmelant, M., 371
Feindel, W., 195*
Fingerhood, S., 182*
Foekler, F. H. Jr., 239
Franklin, D. A., 446
Frederick, W. L., 185*
Freeman, J. H., 413‡
Fruin, R. C., 187*

G

Gabrieli, E., 216*
Galey, D., 186*
Gass, H., 181*
Gibbs, W. D., 18
Gibson, K., 83‡
Goldstein, J. H., 199*
Gorten, R. J., 485
Gottschalk, A., 326
Green, J., 210*
Greenberg, E., 194*
Greenlaw, R. H., 202*
Grenier, J. F., 82‡
Grodsky, G. M., 83‡

H

Hagerdorn, A. B., 208*
Halaby, F. A., 413‡
Halperin, L., 210*
Halva, C. J., 186*
Hardy, E. P., 214*
Harper, P. V., 189*, 277
Harris, C. C., 183*
Hartfield, J. E., 249
Hashizume, A., 333‡
Hatano, M., 82‡
Hayden, H. H., 184*
Hayder, C. J., 332‡
Hayes, R. L., 208*
Haynie, T. P., 85, 193*
Hendrik, J. S., 185*
Hine, G. J., 181*, 371, 439
Hlad, C. J., 159
Hollander, W., 413‡
Holloway, J. E., 296
Holmes, G. W., 345
Holzman, G. B., 212*
Honda, T., 188*
Horwitz, H., 426
Hosick, T., 70
Howe, C. T., 469
Hudspeth, S. A., 200*
Hughes, H. M., 485
Hugh-Jones, P., 82‡
Hulit, H., 203*
Hunter, O. B. Jr., 239
Hutson, W., 453

I

Ihnen, M., 211*
Iio, M., 190*, 212*, 213*
Ilias, K., 198*
Izenstark, J. L., 320

J

Jaffe, H. L., 201*
Janower, M. L., 290
Joftes, D. L., 143
Johnson, D. E., 184*, 193*, 209*, 404
Johnson, L. E., 193*
Johnson, P. C., 106, 139, 195*, 211*, 212*, 393
Jona, J., 195*
Jordan, J. C., 183*
Juda, A., 216*
Jude, J. R., 213*

K

Kaplan, E., 217*
Kaplan, H. S., 193*, 209*
Kariv, I., 197*
Kawin, B., 182*
Kearns, J. E., 453
Keller, L. S., 205*
Kelsey, D., 211*
Kelsey, M. P., 249
Kennady, J. C., 184*
Kenny, P., 194*
Kereiakes, J. G., 426
Kerr, F. W. L., 185*
Kirby, V. V., 185*
Kitano, M., 213*, 214*, 231
Knickerbocker, G. G., 213*
Knorpp, C. T., 188*
Kofman, S., 9
Koplowitz, J. M., 183*
Kotlowski, B., 217*
Kostamis, P., 198*
Kozoll, D. D., 60
Kretchmar, A., 197*
Kyker, G. C., 188*

L

Lachance, P., 186*
Lahr, T. N., 186*
Landauer, R. S., 345
Lankau, C. A., 202*
Lanz, H., 205*
Laor, Y., 193*
Lathrop, K. A., 189*, 277
Laughlin, J., 194*
Lawrence, J. H., 92, 187*, 199*
Leiner, G. C., 78
Lestina, J., 207*
Levitt, S. H., 190*
Levy, L. M., 181*
Lichtlen, P. R., 213*
Lideen, K., 83‡
Lipscomb, A., 132
Littman, A., 187*
Littman, M. S., 187*
Loken, M. K., 234
Loughman, W. D., 187*
Lubin, E., 35

M

MacIntyre, W. J., 189*, 217*
MacDonald, E. J., 249
Madoff, I. M., 413‡
Makowski, E. L., 332
Malamos, B., 198*
Malkasian, G. D., 208*
Malsky, S. J., 204*, 204*
Mannard, J., 188*
Markovich, E. P., 462
Martinez, J., 190*
Masahiro, I., 190*, 213*
Matthews, C. M. E., 82*
McAdams, G. B., 192*
McFee, A. S., 234, 332‡
McAfee, J. G., 190*, 210*
McCardle, R. J., 189*

McEvoy, R. K., 202*
McLeay, J. F., 382
Meade, R. C., 446
Mena, I., 259
Meredith, M., 201*
Merlino, M., 194*
Meschan, I., 70
Meyer, K. A., 60
Miale, A., 195*
Miller, E., 159
Miller, W. N., 78
Morrison, R. T., 162
Moulopoulos, S., 198*
Mozley, J. M., 191*
Murphy, B. P., 333‡
Myers, W. G., 182*, 202*

N

Naumoff, N., 196*
Nelp, W. B., 216*
Nelson, B. M., 208*
Nelson, R. S., 206*
Nerlishi, S., 333‡
Niitani, R., 333‡
Nishiyama, R. H., 167‡
Nordyke, R. A., 215*

O

Oda, F. T., 18
Odell, R. M., 320
Odom, D. D., 211*
Ogborn, R. E., 382
Okezie, O., 181
Okogbue, O., 181*
Oldendorf, W. H., 213*, 214*, 231, 399
Olejar, M., 202*

P

Parker, H. G., 199*
Paraschou, E., 198*
Patno, M. E., 117
Pattee, C. J., 333‡
Paul, W., 1
Peng, C. T., 83‡
Pircher, F. J., 44, 117
Pitlyk, P. J., 185*
Pollycove, M., 187*
Pories, W. J., 202*
Potchen, E. J., 203*, 480
Pyzikiewicz, T., 216*

Q

Quinn, J. L., 200*

R

Rabinowitz, D., 212*
Rabinowitz, J. L., 139, 216*
Rafter, J. J., 188*
Rawalay, S. S., 198*
Ray, R. D., 9
Razzak, M. A., 189*, 206*, 244
Reba, R. C., 191*, 210*
Redding, T. R., 195*, 393
Reid, B., 204*
Reinfrank, R. F., 192*
Rennie, M. H., 188*
Resnick, M. R., 186*
Riley, F. W., 185*
Rivera, J., 214*
Rose, R. G., 206*, 249
Rose, R. S., 218*
Roswit, B., 204*, 204*
Routh, J. I., 162
Rowalay, S., 198*
Rubin, P., 190*, 210*
Rumin, N., 195*
Ryan, J. P., 186*

S

Saenger, E. L., 426
Saito, H., 199*
Samachson, E., 214*
Sanska, R., 83‡
Santchi, D. R., 207*
Sargent, T. W., 199*
Schapiro, R. L., 217*
Schlegel, J. U., 320
Schmid, H., 70
Schmidt, R. W., 167‡
Scholer, J. F., 192*
Scudamore, H. H., 207*
Sedlack, R. E., 185*
Seitzman, D. M., 418‡
Selkirk, T. Jr., 426
Setterfield, M. M., 183*
Shapiro, B., 139
Shuman, L. H., 417
Siemans, W. D., 277
Simkin, S., 212*
Sinna, I. A. A., 184*
Siragusa, J., 239
Sklaroff, D. M., 194*
Sklaroff, J., 216*
Sky-Peck, H., 9
Small, M. J., 78
Smith, E. M., 191*
Socolow, E. L., 333‡
Sodee, D. B., 185*, 190*, 194*, 335
Spencer, H., 214*
Spencer, R. P., 201*
Spreckles, C., 204*
Spring, M., 196*
Stang, L. G., 54
Stanton, L., 417
Steinkamp, R. C., 92
Stern, H. S., 203*
Strain, W. H., 202*
Strauss, H. D., 78
Sullivan, M. A., 216*
Svien, H. J., 185*
Svoboda, A. C., 193*

T

Tabern, D. L., 210*
Taplin, G. V., 184*, 193*, 209*, 404
Taplits, S., 209*
Tauxe, W. N., 185*, 185*, 207*, 208*
Taylor, S. G., 9
Thibaudeau, Y., 9
Thoma, G. E., 215*, 359
Thomsen, P., 259
Tubis, M., 198*
Tucker, W. D., 54
Turner, A. J., 132

U

Udekwu, F. A., 60
Ueda, K., 213*

V

Valee, A. F., 186*
Van Buren, H. C., 167‡
Van Middlesworth, L., 132
Veatch, R., 217*
Veda, K., 213*

W

Wade, L., 195*
Wade, N. M., 78
Wagner, H. N., 190*, 191*, 210*, 212*, 213*, 216*
Walker, J. Z., 207*
Wangensteen, O. H., 332‡
Wase, A., 29
Watson, B. T., 306
Watts, F. C., 70, 200*
Weber, D., 194*
Wegst, A. V., 45
Weiner, I. M., 190*
Weinhold, P., 215*, 359
Weiss, A. G., 82‡
White, R., 413‡
Whitley, J. E., 200*
Wiegel, H. W., 159
Winchell, H. S., 187*
Woodward, I. C., 296
Workman, J. B., 183*

Y

Yamamoto, L., 195*

Z

Zierler, K. L., 212*
Zuidema, G. D., 193*

SUBJECT INDEX

*Indicates abstracts of papers presented at 10th Annual Meeting of Society of Nuclear Medicine.
‡Indicates abstracts from *Current Literature*.

A

Activation Analysis
  Protein bound iodine in plasma by, 191*
  Use of I^{131}, 167‡
  Use of computers in, 306
Angiotensin, labelled with I^{131} and tritium, 332‡
Antipyrine, metabolic fate in human, 216*
Arsenic 74, brain tumor localization with, 1
Autofluoroscope, for renal and cardiac dynamics, 186*

B

Benzoic acid, iodinated for liver Fcn., 198*
Bilirubin, tritiated, preparation and physiological studies, 83‡
Blood
  Changes after I^{131} therapy of thyroid carcinoma, 85
  Elasticity of cranial pool, 214*
  Erythrocytic factors in dogs, 208*
  Flow by Kr^{85} and Xe^{133} in coronary, liver and brain, 213*
  Iron binding capacity in pregnancy, 208*
  P^{32} treatment of chronic lymphocytic leukemia, 92
  Plasma corticoid analysis, 333‡
  Red cell survival in cancer, 207*
  Volume determinations in emergencies, 184*
  Volume determinations in a general hospital, 211*
Blood vessels
  Portal red cell and plasma circ. time in dogs, 296
  Retention of radioisotopes by, 202*
Body water, determination with tritium oxide, 60
Bone
  Metabolism studies with Ca^{47} and Sr^{85}, 194*
  Metastases evaluated with Sr^{85}, 9
  Retention of radioisotopes by, 202*
  Scanning with F^{18} and Sr^{87m}, 193*
  Scanning with Sr^{85} for metastases, 194*
  Sr^{87m} in healing of fractures in rats, 202*
Brain
  Arterio-venous transit time with serum albumin, 214*
  Cerebral blood flow with Kr^{85} and Xe^{133}, 213*
  Cerebrogram for intracerebral disease, 184*
  Comparison of RISA and Hg^{203} in scanning, 195*
  Elasticity of blood pool, 214*
  Neutron dosimetry, 205*

Permeability to labeled compounds of gamma emitters, 213*
Scanning with Hg^{197}, 335
Scanning with Hg^{197} neohydrin, 185*
Brain tumors
As^{74} for localization of, 1
Localization with I^{131} PVP, 185*
Localization with positron scintillation camera, 326
Bromine-82, bromide space for extracellular fluid volume, 469

C

Calcium-45, tooth movement in dogs, 216*
Calcium-47, calcium metabolism, 194*
Cancer
I^{131} for treatment of, 183*
Multiple organ screening with radioautography, 332‡
Red cell survival in, 207*
Carbon-14
Acetate in metabolic defect of thyroid, 195*
Glucose oxidation blood in thyrotoxicosis, 393
Intestinal transport of labeled ascorbic acid, PAB, protein, 201*
Cesium-134
In man, 83‡
Microspheres in intralymphatic admission, 188*
Uptake in normal and infarcted myocardium, 200*
Chromium-51
Erythrokinetics in postgastrectomy, 207*
Portal circulation times in dogs, 296
Cobalt-57, erythrokinetics in postgastrectomy, 207*
Cobalt-60
Direct assay in large urine volumes, 217*
Intestinal transport of B_{12}, 201*
Treatment of equine carcinoma, 184*
Colloid, particle size effect on R.E.S. clearance, 217*
Computers
Analog for radioiodine tracer in thyroid, 197*
Analysis of renogram with, 371
Digital for radioactivity calculations, 463
In activation analysis, 306
Use with scanning data, 182*
Corticoids, plasma analysis of, 333‡

D

Disease, definition preclinical disease, 196*
Dosimetry
In-vivo, radiophotoluminescent, 204*
Of neutrons in head, 205*
Thermoluminescent method, 204*

E

Esophagus, P^{32} tumor detection with G-M counter, 206
Extracellular fluid, bromide space for, 469
Eye
Equine cancer treated with Co^{60}, 184*
Exopthalmos, metabolic defect in, 195*
Strontium-90 application, 184*
Tumor localization with Hg^{203}, 194*

F

Feces, measurement of gamma emitting isotopes in, 332‡
Fluorine-18, bone scanning with, 193*

G

Gallium-68, brain tumor localization with scintillation camera, 326
Glucose, labeled, blood oxidation in thyrotoxicosis, 393
Gold-198
Colloid particle size effect on R.E.S. clearance, 217*
Compared to Au^{199} in liver scanning, 189*
In rat liver tumors, 18
In liver tumors, 188*
Microspheres for intralymphatic therapy, 186*
Microspheres—uses and properties, 186*
Radioactive seeds in neoplasm, 186*
Reticulum cell sarcoma response to colloid, 190*
Scanning of amebic abscess and hydatid liver cyst, 35
Gold-199, compared to Au^{198} in liver scanning, 189*

H

Hair, retention of radioisotopes by, 202*
Heart
Autofluoroscope for dynamics of, 186*
Circ. studies in cor pulmonale of bilharziasis, 206*
Coronary blood flow by external scintillation detection, 259
Coronary blood flow with Kr^{85} and Xe^{133}, 213*
Coronary collaterals in dogs studied with microspheres, 201*
Cs and Rb uptake in normal and infarcted myocardium, 200*
Extrapolation of precordial counting curves, 485
Failure, mercaptomerin absorption and excretion in, 29
K^{40} cardiac muscle, 197*
Myocardial blood flow by Na. I^{131} disappearance, 413‡
Rb^{86} distribution in dog heart, 198*
Renogram and cardiac studies with single probe, 210*
Hippuran, I^{131}
Stability of I^{131}-O-Hippurate, 155
Variation in renal clearance with, 70

I

Infants, newborn, thyroid uptake I^{131}, 162
Insulin, I^{131} preparation of high specific activity, 83‡
Intestine
Completeness of stool collection with La^{140}, 208*
I^{131}, triolein and oleic acid absorption, 82‡
Transport of radiolabeled vitamins, 201*
Iodine-125
Inorganic in radioiodinated, 203*
Production and use, 277
Use of for pulmonogram, 78
Iodine-129, natural occurrence and tracer use by activation analysis, 167‡
Iodine-131
Albumin colloidal for gastric scans, 193*
Albumin for cerebral arterio-venous transit times, 214*
Albumin in rat liver tumors, 18
Antipyrine metabolism, 216*
Blood changes after I^{131} therapy of thyroid cancer, 85
Brain permeability of hippuran, rose bengal, albumin, 213*
Brain tumor localization with PVP, 185*
Conversion ratio by ultra filtration method, 195*
Diagnostic score for hippuran renograms in hypertension, 211*
Ethiodol for therapeutic lymphangiography, 413‡
Hippuran renogram, analysis of, 371
Hippurate renogram in insufficiency after vascular surgery, 106
Hippuran renogram, quantitative aspects, 117
Incidence of thyroid tracers, 290
Inorganic in radioiodinated pharmaceuticals, 203*
Insulin, high specific activity, 83‡
Liquid scintillation counting of, 426
Liver function related to thyroxine metabolism, 132
Low PBI in euthyroids after therapy, 167‡
Placentography with RISA, 417
Portal circulation times in dogs, 296
RISA compare to Hg^{203} in brain scan, 195*
RISA in circulation studies of cor pulmonale of bilharziasis, 206*
Rose bengal in rat liver tumors, 18
Sodium iodide for myocardial blood flow, 413‡
Stability of O-Hippurate, 155
Standardized Hippuran renograms, 446
Tetracyclines, distribution in animals, 382
Thyroid function evaluated by Sephadex test, 139
Thyroid uptake of I^{131} in newborn, 162
Thyroxine analogues across placenta, 453
Treatment of thyroid cancer with, 183*
Triolein and oleic acid absorption, 82‡
Using I^{125}, 78
With albumin, 296
Iron-59
Completeness of stool collection with La^{140}, 208*
Distribution in rat after oral ferrocene, 199*
Erythrokinetics in postgastrectomy, 207*
Iron binding capacity in pregnancy, 208*
Whole body loss, 199*

K

Kidney
Autofluoroscope for dynamics of, 186*
Diagnostic score for renograms in hypertension, 211*
Effect of stop flow to renal scans, 320
Glomerular filtration rate with labeled vitamin B-12, 216*
Hg^{203} labeled neohydrin, stability of, 410
Hippurate, stability of, 155
Quantitative aspects of renogram, 117

Quantitative renogram for renal blood flow, 404
Rate uptake Hg^{203} chlormerodrin for unilateral dis., 210*
Renal plasma blood flow with radiohippuran, 209*
Renogram and cardiac studies with single probe, 210*
Renogram in abnormal radiation therapy, 210*
Renogram in insufficiency after vascular surgery, 106
Renogram, in-vitro analysis of, 45
Renogram, standardized hippuran, 446
Renogram, four channel recording and digital analysis, 371
Scanning with Hg^{197} neohydrin, 335
Scanning with Hg^{203} neohydrin, 185*
Screening of unselected hypertensives by renogram, 215*
Uptakes and scans with Hg^{197} and Hg^{203} neohydrin, 190*
Variation in renal clearance with I^{131} hippuran, 70
Krypton-85
For coronary hepatic and cerebral blood flow, 213*
For pulmonary function, 345

L

Lanthanum-140, for completeness of stool collection, 208*
Leukemia, P^{32} treatment of chronic lymphocytic, 92
Liquid scint. counting
Amebic abscess and hydatid cyst by Au^{198} scan, 35
Of I^{131}, 486
Total body water with tritium oxide, 60
Liver
Au^{198}, rose bengal and Mo^{99} in liver scanning, 188*
Blood flow in schistosomiasis, 189*
Blood flow with Kr^{85} and Xe^{133}, 213*
Function related to thyroxine metabolism, 132
Function with iodinated benzoic acid, 198*
Metabolic rate of I^{131} antipyrine, 216*
Portal hypertension test with I^{131} iodopyracet, 212*
Rat tumors isotope distribution in, 18
Red cell and plasma portal circ. time in dogs, 296
Scanning with Au^{198} and Au^{199}, 189*
Scanning with Hg^{197} Cl, 335
Scanning with Tc^{99m}, 189*
Tritium labeled bilirubin, 83
Lung
Pulmonary function with Kr^{85}, 345
Radiopulmonogram using I^{125}, 78
Xe^{133} for regional function, 82‡
Lymphatics
Administration of radiosotopes, 188*
Infusion of radioisotopes for therapy, 186*
Lymphangiography for therapy, 413‡

M

Mercaptomerin, Hg^{203} absorption and excretion in heart failure, 29
Mercury-197
Kidney uptakes and scans with, 190*
Neohydrin in brain scans, 185*
Scanning with, 335
Mercury-203
Brain permeability of neohydrin, 213*
Chlormerodrin rate uptakes for unilateral renal disease, 210*
Kidney uptakes and scans with, 190*
Mercaptomerin absorption and excretion, 29
Neohydrin for eye tumor localization, 194*
Neohydrin for kidney scanning, 185*
Renogram and cardiac studies with single probe, 210*
RISA compare to Hg^{203} in brain scan, 195*
Spleen scanning with BMHP, 190*
Stability of labeled neohydrin, 410
Microspheres
Intralymphatic administration of, 188*
Intralymphatic for therapy, 186*
Radioactive ceramic—uses and properties, 186*
Use in studying coronary collaterals in dogs, 201*
Molybdenum-99
In liver tumors, 188*
Tc^{99} daughter in liver scanning, 189*

N

Neutron, penetration in phantom head, 205*

O

Oleic acid, I^{131} and triolein absorption, 82‡

P

Pancreas, diagnosis by photoscanning, 193*
Parathyroid
Labeling with H^3 methionine in rat, 480
Selective isotope labeling, 203*
Phosphorus-32
Chromate, colloid particle size, effect on R.E.S. clearance, 217*
In treatment of chronic lymphocytic leukemia, 92
Tumor detection in intestinal tract, 206*
Placenta, transmission of thyroxine analogues, 453
Plastic phosphors, use for gamma emitters in feces, 332‡
Placentography, with RISA I^{131}, 417
Positron emitters, brain tumor localization with positron emitters, 326
Potassium-40, cardiac muscle, 197*
Pregnancy, iron binding capacity in, 208*

R

Radioactivity, digital computer for calculation of, 462
Radioautography
Cancer screening in multiple organs, 332‡
Principles and procedures, 143
Thorium deposits, 205*
Radiosotope, renogram, in-vitro analysis, 45
Radiophotoluminescence, in-vivo dosimetry with, 204*
Radiopulmonogram, 78
Rate meter, with low pass filter, 399
Rates, principles of, 209*
Rectum, P^{32} cancer detection with gas tube, 206*
Reticuloendothelial, effect of colloid particles size on clearance, 217*
Rhodium, Ru-Rh^{106} irradiation of stomach, 187*
Rubidium
Distributed in dog heart, 198*
Uptake in normal and infarcted myocardium, 200*
Ruthenium, Ru-Rh^{106} irradiation of stomach, 187*

S

Scanning
Au^{198}, rose bengal, and Mo^{99} in liver tumors, 188*
Bone metastases with Sr^{85}, 194*
Bone with F^{18} and Sr^{87m}, 193*
Brain tumor with As^{74}, 1
Calcium metabolism with Ca^{47} and Sr^{85}, 194*
Color-coded digital printout for, 439
Color-coded printout, 181*
Consideration of low energy gamma emitters, 183*
Follow-up of amebic abscess and hydatid liver cyst, 35
For liver function using thyroxine, 132
Gastric with colloidal radioalbumin, 193*
Hg^{197} compounds for, 335
Improved quantum utilization, 181*
Kidney, effect of stop flow on, 320
Kidney with Hg^{197} and Hg^{203} neohydrin, 190*
Kidney with Hg^{203} neohydrin, 185*
Of brain with Hg^{197} neohydrin, 185*
Of liver comparing Au^{198} and Au^{199}, 189*
Of liver in schistosomiasis, 189*
Of liver with Tc^{99m}, 189*
Pancreas with Se^{75} methionine, 193*
Spleen with Hg^{203} BMHP, 190*
Stereohepatoscannography, 35
Stereoscans, 181*
Three dimensional, 181*
Transmission of data using computer, 182*
Use of I^{131} PVP for brain, 185*
Schistosomiasis, hepatic blood flow and scanning in, 189*
Scintillation camera
Brain tumor localization with positron emitters, 326
For studies of dynamic processes, 182*
Selenium-75
Analogues of biologically active sulfur compounds, 331‡
Methionine for parathyroid, 203*
Pancreatic scanning with methionine, 193*
Sodium-22, in sweat, 159
Spleen
Scanning with Hg^{197} Cl, 335
Scanning with Hg^{203} bromomercurihydroxypropane, 190*
Stomach
Erythrokinetics in postgastrectomy, 207*
Gastric scans with colloidal radioalbumin, 193*
Radiation of ulcer cancer with Ru-Rh^{106}, 187*
Strontium-85
Bone metastases by scanning, 194*

Calcium metabolism, 194*
For evaluation of bone metastases, 9
Strontium-87M
Bone scanning with, 193*
Healing of rat bone fractures, 202*
Strontium-90
Application in ophthalmology, 184*
Human metabolism with low Sr^{90} uptake, 214*
Y-90 milking device, 54
Sweat, sodium 22 in, 159

T

Technetium-69M, in liver scanning, 189*
Tetracyclines, distribution of iodinated compounds in animals, 382
Thermoluminescence, use in dosimetry, 204*
Thorium, radioautography of tissue deposits, 205*
Thyroid
Analog computer simulation for iodine tracer, 197*
Calibration and standardization of radioiodine uptake, 331‡
Cancer, association with childhood irradiation, 249
Cancer incidence at Hiroshima and Nagasaki, 333‡
Cancer treatment with I^{131}, 183*
Carcinoma blood changes after I^{131} therapy, 85
Carcinoma in children and adolescents, 167‡
Effect of plasma on I^{131} uptake in chick embryos, 312
Function using Sephadex chromatography, 139
Glucose-1, C^{14}, blood oxidation in, 393
Incidence of I^{131} tracers, 290
Low PBI in euthyroids after I^{131} therapy, 167‡
Metabolic defect in exopthalmous, 195*
Potassium iodide compared to T-3 in suppression test, 196*
Protein bound iodine by activation analysis, 191*
Resin sponge modification of T-3 test, 192*
T-3 uptake with dry resin, 215*
Thyrobinding compared with PBI, 192*
Thyroxine analogues, placental transmission, 453
Thyroxin protein association study, 359
Triiodothyroidism—clinical problems, 191*
Ultra filtration wetted for conversion ratio, 195*
Uptake of I^{131} in newborn, 162
Thyroxine I^{131}
Analogues and isomers across placenta, 453
For liver function, 132
Tooth, movement in dogs using Ca^{45}, 216*
Triolein I^{131}, and oleic acid absorption, 82‡
Tritium
Bilirubin labeled with, preparation and physiological studies, 83‡
Intestinal transport of pyridoxin, vitamin D, 201*
Methionine as rat parathyroid label, 480
Total body water determination with oxide, 60

V

Vitamin B-12, glomerular filtration rate with, 216*
Vitamins, radiolabeled, intestinal transport of, 201*

W

Water, total body determination with tritium oxide, 60
Whole body counter
Cesium-134 assay in man, 83‡
Fe^{59} loss, 199*

X

Xenon-133
For coronary hepatic and cerebral blood flow, 213*
For regional lung function, 82‡

Y

Yttrium-90
Chelates in intralymphatic administration, 188*
From Sr^{90} by milking device, 54
Microspheres for intralymphatic therapy, 186*

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11th Annual Meeting
The Society of Nuclear Medicine

San Francisco Bay Area—Claremont Hotel
Berkeley, California—June 17-20, 1964

CALENDAR OF EVENTS

Date	*Name of Course or Meeting*	*Place*
November, 1963		
17-22	Radiological Society of North America	Chicago, Illinois
18-21	Joint Winter Meeting of the American Nuclear Society and the Atomic Industrial Forum and Atom Fair	New York, New York
December, 1963		
19-20	Symposium on Radiation Emergencies in Medicine, Research, and Industry	Chicago, Illinois
19-21	Meeting of the American Physical Society	Pasadena, California
January, 1964		
8-11	6th International Symposium on Radioactive Isotopes in Clinical Medicine and Research	Bad Gastein, Austria
20-23	Hahnemann Medical College and Hospital "Cardiovascular Drug Therapy"	Philadelphia, Pennsylvania
22-25	Meeting of the American Physical Society	New York, New York
February, 1964		
5-8	American College of Radiology	Tucson, Arizona
March, 1964		
6-8	Southwestern Chapter—Society of Nuclear Medicine	Houston, Texas
9-13	5th Inter-American Symposium on Peaceful Application of Nuclear Energy	Chile
April, 1964		
13-16	Annual Meeting of the American Radium Society	White Sulphur Springs, West Virginia
19-21	Second Annual Oak Ridge Radioisotope Conference	Gatlinburg, Tennessee
20-24	Symposium on Medical Radioisotopes Scanning	Athens, Greece
May, 1964		
11-16	Symposium on the Assessment of Radioactive Body Burdens in Man	Heidelberg, Germany
25-27	International Conference of the Canadian Nuclear Association. Subject: Power Reactors and Radioisotopes	Toronto, Canada
June, 1964		
14-18	10th Annual Meeting of the American Nuclear Society	Philadelphia, Pennsylvania
17-20	*11th Annual Meeting of the Society of Nuclear Medicine*	*Berkeley, California*
August, 1964		
	8th Inter-American Congress of Radiology	Caracas, Venezuela
May, 1965		
26-28	Southwestern Chapter—Society of Nuclear Medicine	Dallas, Texas
June, 1965		
16-19	*12th Annual Meeting of the Society of Nuclear Medicine*	*Bal Harbour, Florida*

This Calendar of Events will contain basic information on special courses and meetings of interest to members of The Society of Nuclear Medicine. If you desire more complete information, Mr. Samuel N. Turiel, Administrator of The Society will be pleased to supply you with the name and address of the convening body or sponsoring organization, upon receipt of your request.

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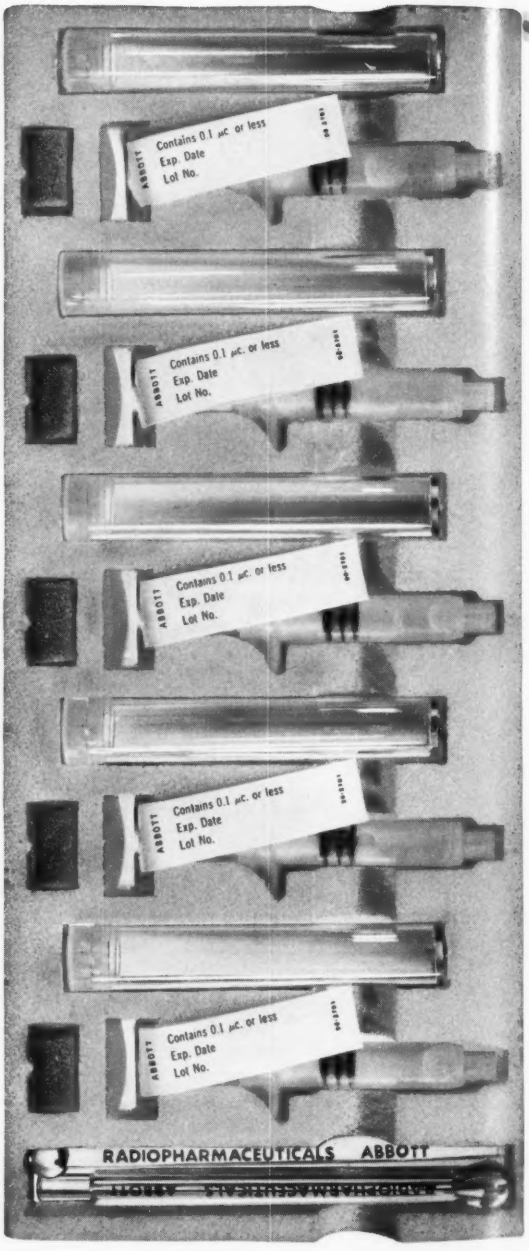

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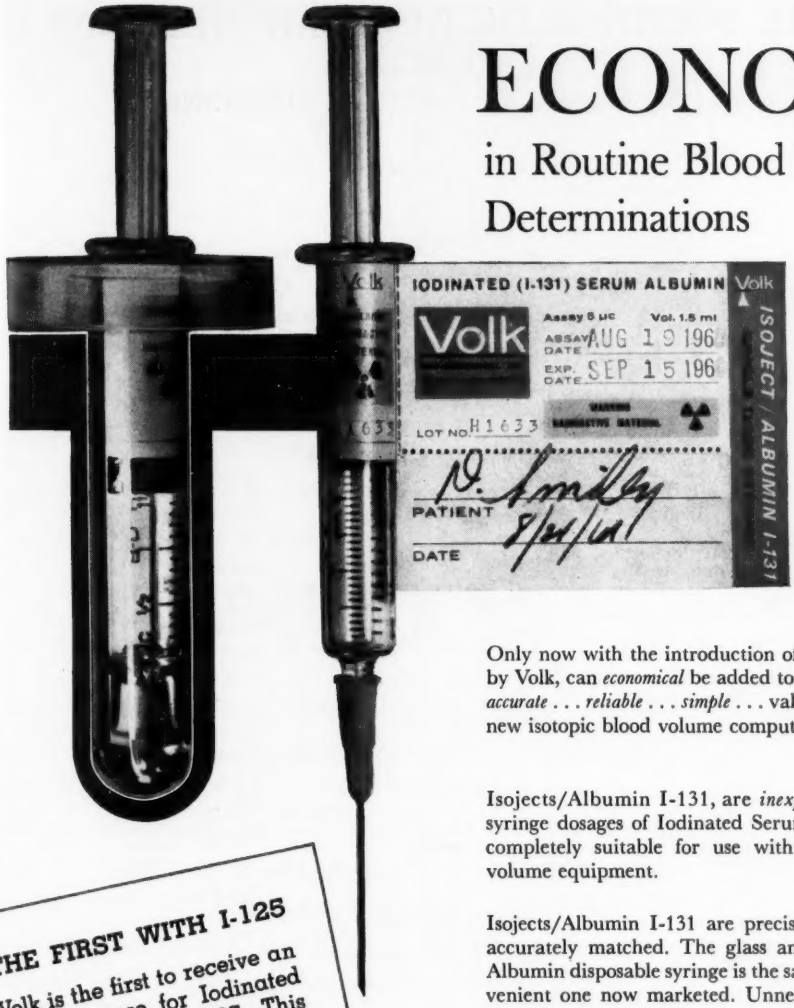

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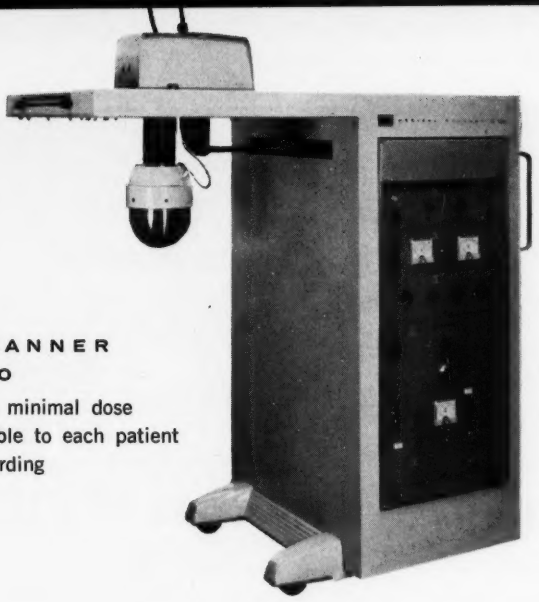

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CONTENTS

Journal of NUCLEAR MEDICINE

VOLUME 4 NOVEMBER, 1963 NO. 6

MILLARD N. CROLL, M.D., LARRY H. SHUMAN, M.D., LEONARD STANTON, M.S. AND CASIMIR CZARNECKI, M.D. Radioisotope Placentograph: A Bedside Procedure. 417

H. HORWITZ, M.D., J. G. KEREIAKES, PH.D., E. L. SAENGER, M.D. AND THEODORE SELKIRK, JR., M.D. Liquid Scintillation Counting of I^{131} in a Clinical Laboratory. 426

GERALD J. HINE, M.D. Color-Coded Digital Print-Out for Radioisotope Scanning. 439

ROBERT C. MEADE, M.S., M.D. AND DONALD A. FRANLKIN, M.D. Results of a Standardized Hippuran Renogram. 446

JOHN E. KEARNS, M.D. AND WILLIAM HUTSON, M.D. Tagged Isomers and Analogues of Thyroxine (Their Transmission Across the Human Placenta and Other Studies). 453

F. S. EBERTS, JR., AND E. P. MARKOVICH. A Digital-Computer Method for Rapid Radioactivity Calculations. 462

C. T. HOWE AND R. P. EKINS. The Bromide Space After the Intravenous Administration of ^{82}Br. 469

E. JAMES POTCHEN, M.D. Isotopic Labeling of the Rat Parathyroid as Demonstrated by Autoradiography. 480

RALPH J. GORTEN, M.D. AND HARRY M. HUGHES, PH.D. Extrapolation of Precordial Counting Curves (Preliminary Progress Note). 485

Index 487

President's Letter vii

Editorial Page ix

First Call for Papers xiii

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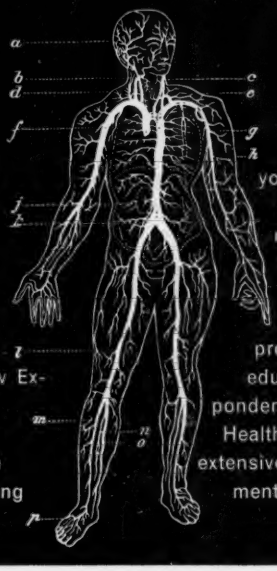

New applications of nuclear energy to the medical instrumentation and X-ray fields and new public health and safety programs offer you additional opportunities for professional growth and increased earnings. CREI's new Extension Program in Health-Physics is planned to prepare you to take advantage of these opportunities—by supplementing your present experience with pertinent knowledge of the nuclear field. This program has been developed in the light of CREI's more than 36 years of experience in providing advanced technical education through the correspondence method. Content of the Health-Physics Program reflects extensive consultation with government and private organizations.

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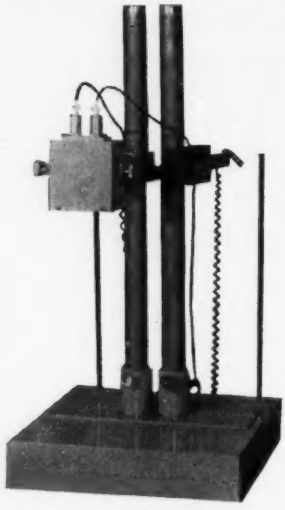

The Detector Positioning Stands shown above are examples of our willingness to cooperate in modifying our standard products for special clinical or research applications.

These stands are our standard Model 69B Detector Positioning Stands, but the shields and detectors are especially designed for measuring radioisotope uptake in dog kidneys.

However, the primary point of this advertisement is to tell more people about our superior, more sturdy, more flexible, easily positioned, reasonably priced, mobile detector positioning stands.

They are available in one-, two-, and three-detector models. The columns and supporting arms are complete, individual units and may be installed in a wide variety of combinations on three different bases. (The two-detector unit shown in the photograph has the columns placed close together, but two other wider spacings are also possible on the same base.)

These detectors positioning stands are built for heavy shields. Detectors three inches in diameter can be shielded with lead two inches thick.

Vertical positioning is precisely controlled by a hand-held switch and electric motor drive. The articulation of the support arms and rotation of the columns permits positioning the detector and shield at any angle.

The low, heavy base assures stability at all times and it rolls easily on heavy, industrial-type, ball-bearing casters.

Dimensions and specifications: over-all height, 62 inches; base height, 7½ inches; detector heights variable 17 to 54 inches above floor; vertical speed, 30 inches per minute; detector extends to 30 inches from column; base dimensions, 24 × 28 inches for single detector model and 28 × 32 inches for multiple detector models; each detector may be positioned completely independently; positive, foot operated floor stops; 110 volt AC power.

Our usual one-year unconditional warranty applies, of course.

If these detector positioning stands might be of interest, we would be pleased to hear from you. Write or telephone collect and talk to Don Steel or Dick Platt (Area Code 216 Number 621-8477).

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President's Letter

THAD P. SEARS, M.D.

Elsewhere in this issue appears the first call for papers to be presented at the 1964 annual meeting of The Society of Nuclear Medicine.

An exact time schedule has been established by the committee for its consideration of papers and the formulation of the final program. Prospective authors should carefully study the announcements and make sure that abstracts are submitted in proper form and in compliance with the time schedule. If there be any questions concerning these matters, a note to Dr. Marshall Brucer will clear them up.

The program as it was given out in preliminary form at Montreal, has been somewhat changed. One of these changes is the omission of the commercial scientific papers which had been planned for the night of June 19.

I think you will find interest in a short analysis of the new program. It is precisely constructed and specifically divided into distinct sections.

Each morning, beginning at 7:30, there will be five 75-minute sessions listed as refresher courses and presented by teachers selected on the basis of skill in their respective fields. These 15 courses are designed to be instructional.

On each of three days from 9:00 AM until noon (one hour excepted on Friday) there will be presented 15-minute papers selected from submitted abstracts and classified under the headings of *diagnostic, therapeutic, preclinical* and *radiobiological* subjects.

Two panel discussions will be given each day on Thursday and Friday afternoons. The four subjects thus considered will be the panels on (1) *Side Effects,* (2) *Diagnostic Advances,* (3) *Spaces and Volumes* and (4) *Therapeutic Advances.* The four panel teams have been chosen as authentic experts. The committee worked with the intent of obtaining panels of a very high order of scientific proficiency.

On Saturday afternoon there will be offered a whole series of ten-minute papers selected from those submitted under the heading of works-in-progress. This type of program is an innovation in the Society that should be of great interest and value. We particularly urge you to attend this session.

In summary, you will note that this program meets the needs of the membership at every level of interest. The program will also be noteworthy in that, except for the refresher courses and one panel session, no two sessions are being simultaneously presented.

This last feature has been hotly debated. Some of the lads say absolutely yes; some say absolutely no; and so who has the answer. Personally I go along with the committee. This program as it is now designed, is uniquely balanced in a manner that could not have been achieved had it been founded on a great multiplicity of papers, sessions and subjects. It is a very rational program obviously destined to make a splendid contribution to the membership.

You must indulge my temptation to say something about this scientific program committee. I have attended all their meetings. Brucer is the chairman; Elrick and Hlad are the other members. Glenn Sheline of the local arrangements committee has and will attend some of their meetings. It is a little unusual that this committee has met, in person, on five occasions and plans several more personal meetings. It is more unusual that they have done this despite two thousand miles of travel for every meeting. And do these fellows ever work for two solid days on each occasion. If it is in fact true that a program will be no better than the committee that forms it, then this program should be a top event of 1964.

There will be much more to say about the Berkeley meeting. You have yet to hear about the local arrangements under Sheline and the attractive prices at a comfortable hotel which we will exclusively occupy.

In the meantime, will not every member please accept this letter as a very personal presidential greeting.

ANNOUNCEMENTS

POSITIONS AVAILABLE AT DONNER LABORATORIES

The Lawrence Radiation Laboratory and Donner Laboratory, University of California, Berkeley, announce an opening for a physician to work in the field of radiation health.

Duties consist of active participation in a health medicine program including problems of occpuational exposure to a wide variety of physical, chemical, and radiation agents. Emphasis is placed on general competency in medicine and research interests and capability. Opportunities are provided for research in radiation health and nuclear medicine, and enrollment in a minimum of courses in the basic sciences can be arranged.

Experience desired:

Approximately 5 years after M.D. degree. Preference will be given to training in pertinent medical specialties or post-doctoral studies, including research.

The Donner Laboratory, University of California, Berkeley, announces an opportunity for participation in biomedical engineering research. Principal problems under study include dosimetry methods of measurement and delivery of radiation under a variety of conditions.

Applicants should have at least a B.S. in engineering physics, electrical or electronic engineering, a minimum of two years' experience in these or related fields, and strong interest in biophysical research. Stipend will depend on training and experience.

For further information and application forms, write to Dr. John H. Lawrence, Director, Donner Laboratory, University of California, Berkeley, California, 94720.

ORINS ANNOUNCES 1964 TRAINING COURSES

The 1964 schedule of training courses in the use of radioisotopes has been announced by the Oak Ridge Institute of Nuclear Studies (ORINS), Oak Ridge, Tenn.

The courses are offered to assist scientific, engineering, technical, and medical personnel in obtaining in a short time sufficient facility in radioisotope techniques and applications to use them safely and efficiently within their individual fields.

Up to 48 participants will be accepted in the four-week courses in radioisotope research techniques and the three-week engineering courses. Courses of varying duration are offered in specific areas of interest in other fields.

The dates for the 1964 courses are as follows: Jan. 6-31, Feb. 10-March 6, Apr. 27-May 22, Sept. 14-Oct. 9 (tentative). Information on these courses, as well as special courses, including those for physicians, may be obtained from Ralph T. Overman, Chairman, Special Training Division, Oak Ridge Institute of Nuclear Studies, P. O. Box 117, Oak Ridge, Tennessee.

ORINS SCHEDULES TRAINING COURSES

The 1964 schedule of training courses in the diagnostic application of radioactive isotopes has been announced by the Oak Ridge Institute of Nuclear Studies (ORINS), Oak Ridge, Tenn.

The courses, administered by ORINS for the U. S. Atomic Energy Commission, are designed to provide minimal basic training and clinical experience in the safe handling of radioactive materials to qualify physicians for AEC licensure to use radioisotopes on patients.

Completion of the courses requires three one-week sequences—basic, preclinical, and clinical—taken either consecutively or in single weeks spaced at the convenience of the applicant. This arrangement is for the benefit of physicians unable to leave their practice for three successive weeks.

Schedule for the 1964 courses are as follows: Basic Week: Jan. 6-10, March 2-6, May 4-8, Sept. 14-18. Preclinical Week: Jan. 13-17, March 9-13, May 11-15, Sept. 21-25. Clinical Week: Jan. 20-24, March 16-20, May 18-22, Sept. 28-Oct. 2.

Information about the courses, fees, and application blanks may be obtained by writing to Dr. Ralph T. Overman, Special Training Division, Oak Ridge Institute of Nuclear Studies, P. O. Box 117, Oak Ridge, Tenn.

EDITORIAL

A Look To The Future OF THE JOURNAL

At the tenth annual meeting of The Society of Nuclear Medicine in Montreal the associate and consulting editors recommended that THE JOURNAL OF NUCLEAR MEDICINE be published on a monthly basis, commencing in January, 1964. This recommendation was overwhelmingly approved by the members in the annual business meeting.

The editorial staff accepts this vote of confidence with humility and with the determination to guide the publication of THE JOURNAL in a manner that will reflect the scientific objectives of The Society and at the same time render greater service to the membership.

The recommendation and decision to add to the already crowded field of medical literature warrants some explanation and discussion.

Over the past several years publication time in THE JOURNAL has been unduly long, because of the backlog of excellent papers. This time will be shortened considerably by monthly publication. Other features; such as scientific editorials and letters to the editor, book reviews, and appropriate Society news; have long been recognized as desirable features, but in the past could not be included in THE JOURNAL because of the unavailability of space.

As an adjunct to the president's newsletters, additional Society information will be communicated to the members at appropriate times through the president's page in THE JOURNAL.

The increased publication rate will provide space for additional abstracts of current articles on the various aspects of nuclear medicine published in other journals as well as for abstracts of papers presented at chapter meetings.

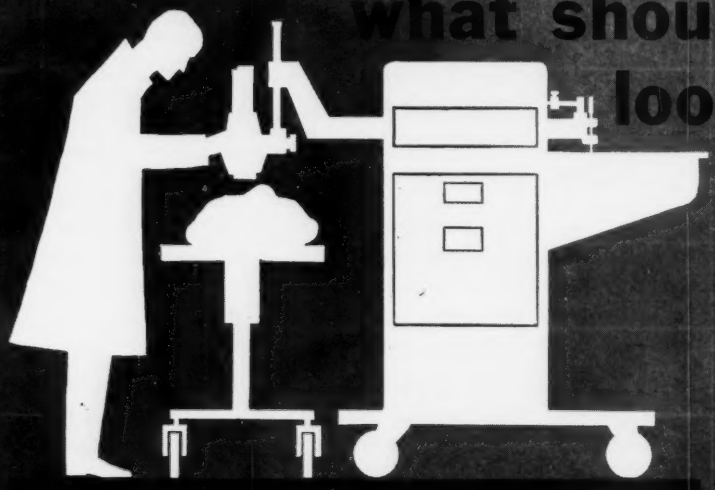
Finally, monthly publication will allow for balance of the subject matter of original articles, permitting the addition of more papers on biological effects of radiation, radiation protection, and instrumentation to the important categories of diagnosis and therapy.

As THE JOURNAL reaches another milestone, the expressed appreciation of the editor for the interest, cooperation, and patience of the members of The Society and their officers is in order. Likewise, it is acknowledged that without the generous assistance of the associate and consulting editors and the reviewers the publication of THE JOURNAL as a scientific periodical would not be possible.

G.E.T.

when investing in a scintillation scanner

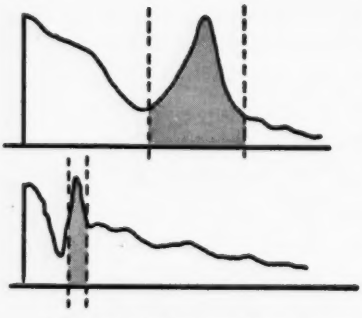
what should you look for?



among other things

flexibility **in choice of isotope**

I^{131} I^{125} Au^{198}
Hg^{203} Hg^{197} Cr^{51} Se^{75}



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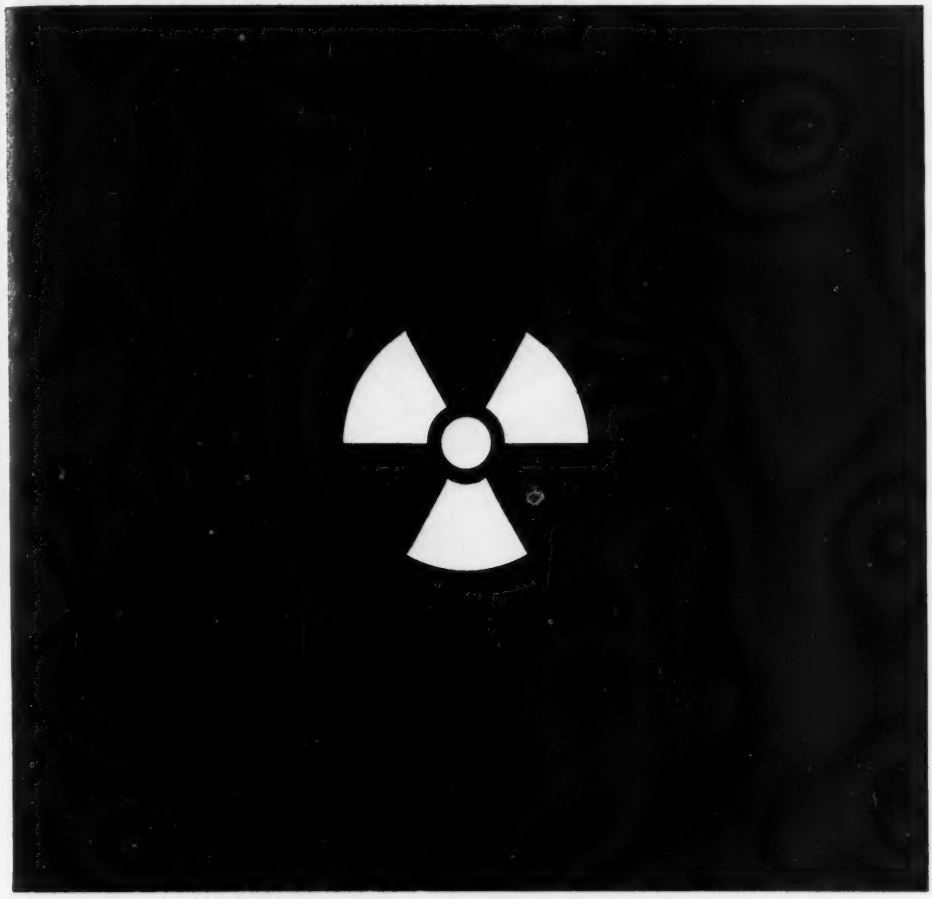

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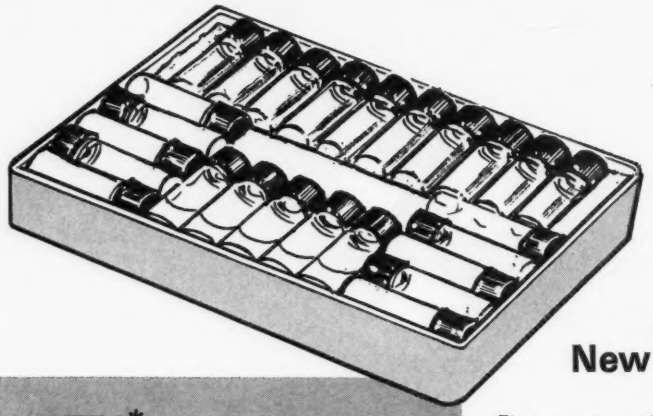

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† J. F. Scholer, M.D.; Palo Alto Medical Clinic

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In February 1964 the Program Committee Will Select Fifteen Minute Original Papers for the Diagnostic, Therapeutic, Preclinical and Radiobiological Sessions.

In April 1964 the Program Committee Will Select Ten Minute Papers for the Works-In-Progress Sessions.

To Be Considered All Abstracts Must Be Submitted With:

Author's Name;	Underline the Author Presenting the Paper.
Title;	Maximum of 10 Words.
Abstract;	Maximum of 300 Words.

Send Abstracts To:

The 1964 Program Committee—Society of Nuclear Medicine

Marshall Brucer, M.D., Chairman

Route 4, Box 203

Tucson, Arizona

SYMPOSIUM ANNOUNCEMENT

On January 30-31, 1964 a Symposium on *Scintiscanning in Clinical Medicine* will be held in Winston-Salem, N. C. sponsored by the Department of Radiology of the Bowman Gray School of Medicine.

Subjects to be covered will include the physical, electrical and pharmacologic principles of organ scanning as well as specific discussions of brain, thyroid, parathyroid, heart, lung, liver, spleen, kidney, pancreas and bone scanning.

The Guest faculty will include Craig Harris, M. S. Oak Ridge; John Hidalgo, M. S. Tulane; John McAfee, M. D. and Henry Wagner, M. D. Johns Hopkins; Merrill Bender, M. D. Roswell Park; David Sklaroff, M. D. Philadelphia; Bruce Sodee, M. D. Walter Reed; William Beierwaltes, M. D. and Edward Carr, M. D. Michigan; Thomas Haynie, M. D. Texas; Joseph Izenstark, M. D. Emory; Albert Gilson, M. D. Miami; Felix Pircher, M. D. Duke; Frances Pepper, M. D. North Carolina; J. M. Miller, M. D. Henry Ford; and I. Meschan, M. D., Joseph Whitley, M. D., and J. L. Quinn, III, M. D. of Bowman Gray.

Registration will be limited to 200. For details write to J. L. Quinn, III, M. D., Nuclear Medicine, Bowman Gray School of Medicine, Winston-Salem 7, N. C.

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Cambridge, Massachusetts iii

Capitol Radio
Engineering Inst.
Washington, D.C. v

Curtis Nuclear
Glendale, Calif. .. Inside Back Cover

Nuclear Consultants
Corporation
St. Louis, Mo. xii

Nuclear, Chicago
Des Plaines, Illinois ..... Back Cover

Ohio-Nuclear
Cleveland, Ohio vi

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New York, New York xi

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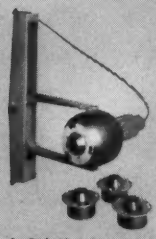

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The design of this remarkable new clinical instrument derives from the work of H. O. Anger at the Lawrence Radiation Laboratory. The Scintillation Camera offers two principal advantages over conventional clinical isotope scanners: (1) completed pictures of radioisotope distribution in organs or body areas are produced in one-tenth to one-twentieth of the time required by conventional isotope scanners, (2) the instrument permits rapid-sequence, stop-motion pictures of dynamic processes such as the flow of labelled compounds into and out of an organ. Prototype models of the Scintillation Camera are now being manufactured by Nuclear-Chicago for several clinical investigators. Prices are in the range of $30,000 for systems including pinhole and multihole collimators, cathode-ray display with multiple-lens self-processing camera, and television viewing system driven by a flying-spot scanner. We have prepared preliminary data sheets on the Scintillation Camera and will be pleased to send you a set if you are interested in learning more about this elegant new method of locating and visualizing the distribution of radioisotopes in the body. Please address your request to John L. Kuranz, vice-president. NUC:D-3-250

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